IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CHUGAI PHARMACEUTICAL CO., LTD., Plaintiff, v. ALEXION PHARMACEUTICALS, INC., Defendant.	C.A. No. 18-CV-1802-MN **CONSOLIDATED**

JOINT CLAIM CONSTRUCTION BRIEF

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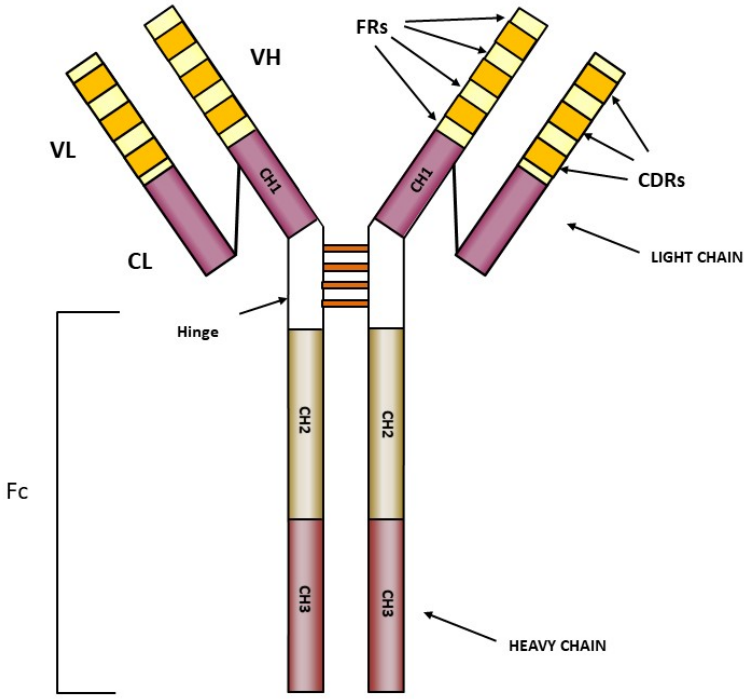
I. CHUGAI'S BACKGROUND OF THE TECHNOLOGY AND THE '377 PATENT

Chugai is a biopharmaceutical company based in Japan that has developed many groundbreaking and life-saving medications. The Chugai inventions relevant to this case are antibody technologies described in and protected by pending patent applications and by U.S. Patent No. 9,890,377 ("the '377 patent"). An antibody is a Y-shaped protein that is used in the immune system to bind to, and thereby neutralize, harmful antigens.[1] (Declaration of John Williams ("Williams Decl.") ¶ 13.) There are naturally occurring antibodies and there are engineered antibodies, including antibodies that have been engineered to include both human and non-human (e.g., mouse, rat) sequences of amino acids. (*Id.* ¶ 14.) A schematic representation of an antibody is shown below:



[1] Antigens are substances, such as viruses, bacteria, blood group proteins, etc., that induce an immune response in the body, often triggering the production of antibodies. (Williams Decl. ¶ 13.)

As shown in the diagram, the antibody consists of two light chains and two heavy chains, which are long chains of amino acids. (Williams Decl. ¶ 15.) Each light chain is composed of a variable region (V_L) and a constant region (C_L), and each heavy chain is composed of a variable region (V_H), a hinge region, and three constant regions (C_{H1}, C_{H2}, and C_{H3}) (*Id.*) The hinge region links the C_{H1} and C_{H2} regions. The C_{H2} and C_{H3} in turn make up the fragment crystallizable ("Fc") region. The variable regions give the antibody its binding specificity for a particular antigen and are further made up of framework regions ("FRs") and complementarity determining regions ("CDRs"). (*Id.*) The FRs essentially provide scaffolding for the CDRs, which are the regions that provide the binding specificity to an antibody. The amino acid sequence of the CDRs can be viewed as comprising a very specific "key" to the corresponding "lock" of the target antigen. (*Id.*) It is the variability in CDRs that result in millions of unique antibodies, including many that have been or will be engineered to facilitate the treatment of disease. (*Id.*)

Antibodies are also known as immunoglobulins. (Williams Decl. ¶ 16.) There are five types or classes of immunoglobulin: IgG, IgA, IgM, IgD and IgE. (*Id.*) Most of the antibodies in the blood are IgG antibodies. (*Id.*) The IgG class of antibodies is divided into four different subclasses of IgG molecules, designated as IgG1, IgG2, IgG3, and IgG4 in humans. (*Id.*)

The '377 patent discloses methods of removing antigens from a patient's blood plasma using antibodies modified to take advantage of the weaker antigen-binding activity at the pH of a cell endosome in comparison with that at the pH of plasma.[2] The modified antibodies are

[2] An endosome is a vesicle within a cell in which material from the cellular surface is sorted and transported. (Williams Decl. ¶ 17.) Blood plasma is the liquid part of the blood that carries cells and proteins throughout the body; it makes up about 55% of the body's total blood volume. (*Id.*) Scientists use pH as a measure of how acidic or alkaline a solution is. (*Id.*) The pH scale usually

capable of recycling such that they repeat the antigen-binding process multiple times rather than a single time.

Chugai's work on the antibody recycling technology described in the '377 patent began before 2010. The '377 patent stems from a series of patent applications claiming priority to a first patent application filed on April 11, 2008. In October 2010, work by Chugai scientists relating to its antibody recycling technology was published in *Nature Biotechnology*. *See* T. Igawa et al., *Antibody Recycling by Engineered pH-Dependent Antigen Binding Improves the Duration of Antigen Neutralization*, Nature Biotechnology, 28 (11):1203-07 (2010). *Nature Biotechnology* is a peer-reviewed scientific journal published monthly by the Nature Publishing Group. It is one of the most frequently cited biotechnology publications in the world. The Chugai article was featured on the cover that month.

In some conventional antibody drugs, the antibodies contained in the medication bind to the harmful antigens, the antibody and antigen are then internalized by the cell endosome, and are then degraded by the cell lysosome. This process often destroys both the antigen and the

ranges from 0 to 14; solutions with pH less than 7 are considered acidic and those above 7 are considered alkaline. (*Id.*)

antibody such that the antibody performs its function only once before being destroyed. Because the antibody is destroyed in this process, patients taking conventional antibody medications require frequent doses to ensure there are a sufficient number of antibodies in the bloodstream. Generally speaking, IgG antibodies are Y-shaped, and each arm of the Y can bind to an antigen. Thus, if one wants to remove one million antigen molecules, one would need at least 500,000 conventional IgG antibodies because one Y-shaped antibody can bind, at most, two antigens.

The ’377 patent teaches methods that allow antibodies to facilitate antigen destruction without also destroying the antibody, such that the antibodies have improved durations of time in which they can bind to antigens. An schematic overview of the process is shown below:

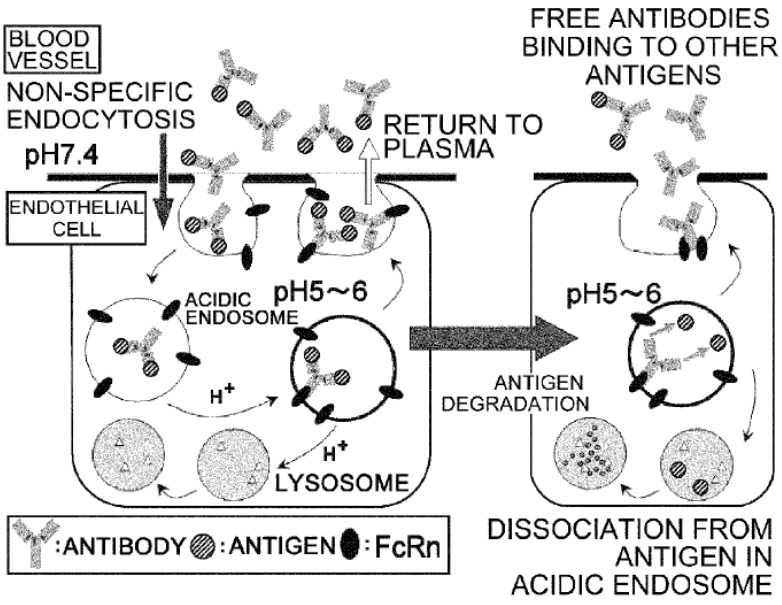


FIG. 4

(Ex. A (’377 patent), Fig. 4.) As shown in the figure, the modified antibodies taught by the claimed invention bind to antigens in the blood plasma (pH 7.4) to form an antibody-antigen complex. The complex is then internalized into a cell endosome (lower pH), where the antibody

portion of the complex binds to the FcRn receptor on the endosomal membrane. The acidic pH of the endosome causes the antigen to dissociate from the antibody, which remains bound to the FcRn receptor. The antigen is subsequently destroyed, while the antibody is recycled back to the plasma to repeat the entire process. Chugai's breakthrough technology allows therapeutic antibodies to be recycled in a patient's body instead of being destroyed, which can dramatically improve the patient's quality of life by decreasing the quantity and frequency of drug treatments needed to manage a disease. If, for example, the antibodies are engineered so they can recycle back into the bloodstream 5 times, removing one million antigen molecules can be accomplished with far fewer antibodies compared to conventional methods.

The inventors characterized an important feature of their invention in terms of the dissociation constant (KD), which is a measurement of the propensity of an antibody to separate from its target antigen, and which can change for a given antibody-antigen pair depending on the pH of the surrounding environment. (Williams Decl. ¶ 19.) Chugai discovered that the ratio of KD values at different pH values, e.g., KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD at pH 5.8 and at pH 7.4, was an important indicator of whether antibody recycling would occur, and Chugai secured claims from the Patent Office that include various KD ratios. Claims 8 and 9, which depend from claim 1, are asserted against Alexion in this litigation.

II. ALEXION'S BACKGROUND OF THE TECHNOLOGY AND THE '377 PATENT

A. Alexion's Development of Anti-C5 Inhibitors for the Treatment of Rare Diseases

Alexion Pharmaceuticals, Inc. ("Alexion") is a global biopharmaceutical company headquartered in Boston dedicated to serving patients and families affected by rare diseases through the discovery, development, and commercialization of life-changing therapies. Through its focus on developing treatments for rare diseases, Alexion developed SOLIRIS®

(eculizumab), the world's first approved complement inhibitor for the treatment of various blood disorders, including paroxysmal nocturnal hemoglobinura (PNH) and atypical uremic syndrome (aHUS). The complement system is part of the human immune system and functions to defend the body against foreign antigen threats. Some persons' blood cells lack natural protections that prevent the complement system from attacking and destroying them. For those persons, a complement inhibitor can protect the blood cells by interrupting the complement system to prevent these cells' destruction.

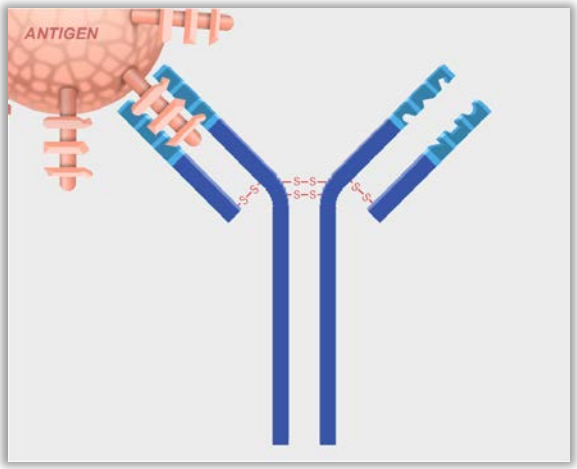
SOLIRIS® is an antibody that binds to C5. C5 is a necessary protein in the cascade that activates the complement system. When SOLIRIS binds, it prevents the cleavage of C5 into C5a and C5b. C5b is a necessary part of the membrane attack complex (MAC), which is directly responsible for the destruction of unprotected blood cells. Declaration of Paul W. H. I. Parren, Ph.D. in Support of Alexion's Answering Claim Construction Brief ("Parren Decl.") ¶¶ 20-22. After developing SOLIRIS, Alexion continued its research to further improve the treatment of patients with rare diseases. More than a decade after bringing SOLIRIS to market, Alexion obtained FDA approval for ULTOMIRIS® (ravulizumab). Like SOLIRIS, ULTOMIRIS is an anti-C5 antibody that inhibits cleavage of C5 into C5a and C5b. SOLIRIS and ULTOMIRIS are the only FDA-approved complement inhibitors for treating PNH and aHUS.

B. Structure and Function of Antibodies

The human immune system comprises multiple pathways to protect the body against foreign invaders. Some of these pathways recognize foreign proteins, called antigens, and produce antibodies that bind to block or remove antigens. Parren Decl. ¶ 23. Countless substances are perceived by the human immune system as antigens. The immune system will generally produce millions of antibodies in response to each antigen. *Id.*; *supra* at 2.

Antibodies have a "Y-shaped" configuration. Parren Decl. ¶ 24. The interaction between

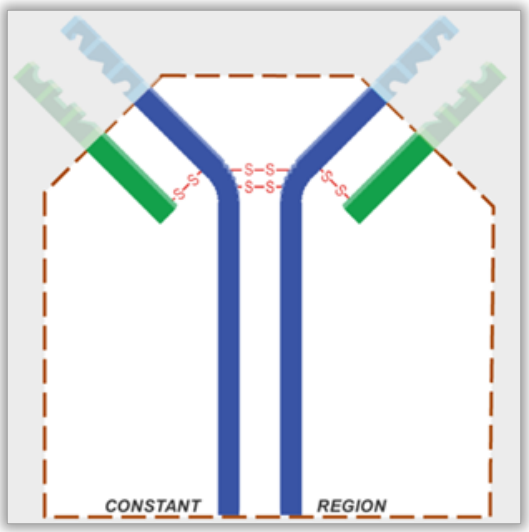
an antibody and an antigen is often described by a lock and key analogy. Like a key, an antibody possesses a specific configuration that allows it to bind with a specific part of an antigen (in this analogy, the lock).

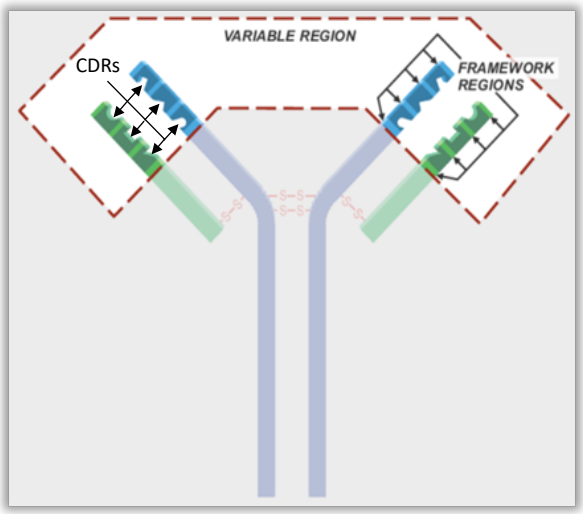


A more appropriate description, however, is a lock (or antigen) that can engage with millions of keys (antibodies). *Id.* Each of these antibodies bind the antigen with different affinities and at different locations—or epitopes—on the antigen. *Id.* The result is that each antibody has a different ability to neutralize the antigen. *Id.*

An antibody consists of two identical heavy chains and two identical light chains. The heavy chain and the light chain each include a variable region and a constant region. Parren Decl. ¶ 25. The variable regions of an antibody include highly variable complementarity determining regions ("CDRs"), a.k.a. hypervariable regions, and less variable framework regions. Parren Decl. ¶ 26. The CDRs are largely responsible for the specificity and affinity of an antibody for its antigen. *Id.* The framework regions function to correctly align the CDRs to allow for interaction with the antigen. *Id.* The variable regions of the heavy and light chains include three CDRs each, such that each arm of the "Y" shape of the antibody includes six unique CDRs: HCDR1, HCDR2 and HCDR 3 of the heavy chain and LCDR1, LCDR2 and

LCDR 3 of the light chain. *Id.*



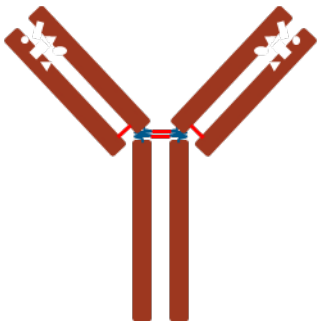


Identifying an antibody with a variable region specific to an antigen is difficult and unpredictable because any change to the amino acid sequence of the variable region, especially in the CDRs, will almost invariably alter the function of the antibody. Parren Decl. ¶ 27. This unpredictability requires scientists to generate and test a very large number of antibodies for any given antigen in the hopes of identifying a handful of antibodies that have desirable properties. *Id.*

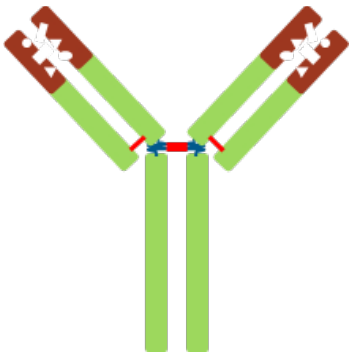
Several methods exist to generate antibodies to an antigen. If the antigen is foreign to a species, e.g., a mouse, the antigen may be injected into the mouse and the mouse will generate mouse (murine) antibodies to that antigen. Parren Decl. ¶ 28. The antibody obtained thereby is a naturally-occurring antibody. An early method of obtaining a human antibody was to isolate antibodies produced by a human in response to a foreign antigen. *Id.* As the technology has progressed, new methods have become available that allow generation of antibodies with human variable regions from non-human sources. *Id.* These methods include inoculating a transgenic animal that comprises human antibody genes, often a mouse, with an antigen. Parren Decl. ¶ 29.

Another method that can generate human variable regions is phage display. Parren Decl. ¶ 30. This method utilizes living cells, such as bacterial cells, that will display variable regions on the bacterial surface when exposed to an antigen of interest. These methods result in naturally-occurring variable regions, because the genetically modified animal or bacteria cell produces the variable regions. Parren Decl. ¶¶ 29-30.

The first medicinal antibodies were murine antibodies. These antibodies had drawbacks. Parren Decl. ¶ 31. Subsequent research addressed these drawbacks by modifying the amino acid sequences of a murine antibody to make the antibody appear more human. *Id*. These antibodies included murine variable regions attached to human constant regions.[3] *Id*. Further progress was achieved by "humanizing" such murine antibodies. Humanized antibodies include both human constant regions and human framework regions (the portion of the variable region between CDRs) while including the useful CDR regions from another species, usually a mouse. *Id*. The antibody engineering field eventually developed to allow manufacture of fully human variable regions that may be combined with fully human constant regions to generate a human antibody. *Id*.

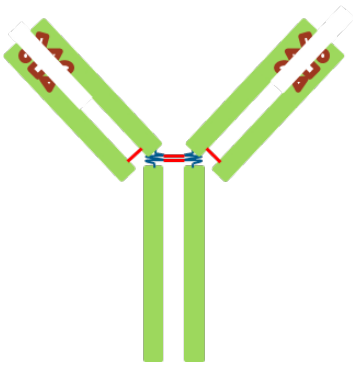


Murine Antibody

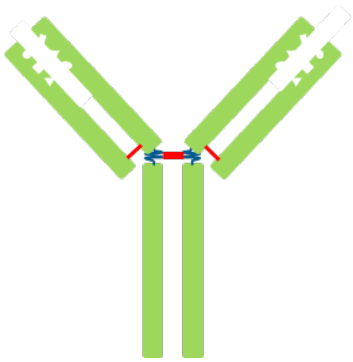


Chimeric Antibody

[3] This is one example of a chimeric antibody. A chimeric antibody is any antibody that includes portions from two species. Parren Decl. ¶ 31.



Humanized Antibody



"Fully Human" Antibody

Once an antibody with the desired characteristics is identified, e.g., an antibody that binds strongly with a target antigen, modifications to the amino acid sequences may be made in an attempt to improve the properties of the antibody. These modifications result in the generation of variants of the previously identified antibody. Parren Decl. ¶ 32. The locations, numbers, and types of modification in a variant may drastically affect the ability of the new antibody to recognize and bind to the antigen of interest. *Id*. The modifications can also impact other important properties of the antibody. *Id*. Modifications to the amino acid sequence of a CDR are known to present the highest likelihood of altering binding for the antigen of interest. Such modifications are highly unpredictable; it is unknown a priori whether a modification will increase, decrease, or not affect binding to the antigen of interest. Parren Decl. ¶ 33. Therefore, through trial and error each variant must be tested to determine its antigen-binding ability and other properties. *Id*.

C. The '377 Patent

The '377 patent purports to describe a method to leverage the propensity of some

antibodies to have differing binding properties for an antigen under different pH conditions.[4] '377 Patent, 9:33-49.[5] The asserted patent claims cover both naturally-occurring and modified antibodies. *Id.* at 171:18-36, 171:63-172:44. With respect to modified antibodies, the '377 patent suggests modifying existing antibodies through substitution of histidine in the variable region to generate a variant of that antibody that has reduced binding affinity for an antigen at acidic pH as compared to the binding affinity at a neutral pH. *Id* at 9:33-49. But this in itself is not novel. Parren Decl. ¶ 35. The '377 patent acknowledges "[i]t is already known that an antibody can be conferred with a pH-dependent binding activity by substituting histidine for amino acids in the antibody. (FEBS Letter, 309(a), 8588 (1992))." '377 patent, 12:63-66. Indeed, the patent concedes that others had succeeded in imparting pH-dependent binding properties to protein-protein interactions, specifically antibody-antigen interactions, by substituting histidine into the CDR sequence of an antibody. *Id*., 58:56-66. In that instance, just as the '377 patent describes, the substitution of histidine decreased the ability of the antibody to bind with the antigen under acidic conditions. *Id*.

Beginning with its original priority patent application, the '377 patent specification applies the prior art teachings concerning histidine's effect on binding under acidic conditions by modifying a known humanized anti-IL-6R antibody designated as PM1. '377 patent, 55:40-51, 60:31-33 (both citing Cancer Res. 1993, Feb. 15; 53(4): 851-6). The patent references PM1 as a wild-type IL-6R neutralizing antibody and uses this antibody as a comparison to antibodies with

[4] Neither the specification nor the claims identify any disease to be treated or antibody dosage amount to be administered, which suggests that the claims encompass methods of administering any antibody having the propensity for pH-dependent binding to any antigen in order to remove the antigen from plasma. Parren Decl. ¶ 34

[5] This notation references column:line numbers. Citations that encompass multiple columns are denoted as column:line-column:line.

histidine substitutions made in the variable regions. '377 patent, 64:54-56, *see also* Table 5, 66:4-18 (comparing WT (PM1) with H3pI/L72, H170/L82 and CLH5/L73). Although the patent discloses a comparison between PM1 and these antibodies to purportedly understand the effect of substituting histidine into the variable regions, these three variant antibodies also include non-histidine mutations in both the heavy and light chain variable regions as compared to PM1. *See infra* at 52, Fn. 19; Parren Decl. ¶ 36. This is confounding, because the effects of the non-histidine substitutions on the variant antibodies' pH-dependent binding behavior are unknown. Parren Decl. ¶¶ 37, 38. Accordingly, one cannot determine from the specification what effects, if any, the histidine substitutions have on the variant antibodies' pH-dependent binding properties. Parren Decl. ¶ 38

Well after the filing date of the original priority application, Chugai submitted other patent applications with additional disclosures. One later application includes testing for two variants of an anti-IL-6 antibody. *See* JP2009-068744 filed March 19, 2009, Example 16, Table 14 (comparing anti-IL-6 antibody variants, i.e., clone 1 and clone 2, to a wild-type antibody for IL-6). An even later application shows testing of "clone 1," a variant of a wild-type antibody for IL-31R. *See* PCT/JP2009/057309 filed April 10, 2009, Example 17, Table 16 (comparing clone 1 to a wild type of IL-31R). The patent, however, provides only *in-vitro* testing for the disclosed IL-6 and IL-31R antibodies, and although the reported data suggest that the variants exhibit pH-dependent binding to the antigen *in vitro*, the '377 patent does not provide any data concerning the ability of these antibodies to remove an antigen from plasma. Parren Decl. ¶ 39.

Certain claims of the '377 patent require starting with an existing antibody and mutating its variable region to generate a variant that has certain properties. '377 patent, claims 11 and 18; Parren Decl. ¶ 40. The properties that the variant antibody must have include: (1) a

KD(pH5.8)/KD(pH7.4) value higher than the parent antibody, (2) a KD(pH5.8)/KD(pH7.4) value between 2 and 10,000, (3) the ability to bind the antigen in plasma, and (4) dissociating from the bound antigen under conditions present in the endosome *in vivo*. '377 patent, 172:20-38, 173:4-25; Parren Decl. ¶ 40. Chugai has not asserted these claims.

Instead, Chugai asserts only claims 8 and 9 of the '377 patent against Alexion's ULTOMIRIS product. Both claims depend from claim 1. Claim 1 purports to describe a method for removing *any* antigen from plasma by administering *any* antibody that binds to that antigen. '377 patent, 171:18-36; Parren Decl. ¶ 41. As Chugai's expert stated in his declaration, there are likely *millions* of unique antibodies to each antigen. *See* Williams Decl. ¶ 15; Parren Decl. ¶ 41. These claims purport to encompass removal of *any* antigen by administering any one of *an unknown number of antibodies* that binds to the antigen and exhibits the claimed functional properties. *Id*. Claim 1 does not require mutating the variable region of an existing antibody through the introduction of histidine to achieve the functional limitations of the claims. Parren Decl. ¶ 42. Rather, claim 1 encompasses within its scope *all* antibodies that meet the functional limitations of the claim, irrespective of whether the antibody exhibits the claimed functionality naturally, whether the antibody achieves the functionality through mutation of any part of its amino acid sequence, or whether the antibody's claimed functionality results from the properties of the antigen, e.g., the amino acid sequence of the antigen causes a change in binding properties under different conditions. *Id*. Despite Chugai's suggestion throughout its brief, asserted claims 8 and 9 are not limited to "modified antibodies." *Supra* at 2 ("The '377 patent discloses methods . . . using antibodies modified . . . . The modified antibodies are capable . . . ."), 4 ("the modified antibodies taught by the claimed invention"); *see also* Williams Decl. ¶¶ 17, 18, 26 ("claimed invention is directed to treatment methods with improved antibodies"); '377 patent, col. 171-172

(compare claim 1 to claim 11). Instead, they encompass all antibodies, whether modified or naturally occurring, that exhibit the claimed functional properties, whether due to their own amino acid sequence or the sequence of the antigen. Parren Decl. ¶ 42.

D. Person of Ordinary Skill in the Art

Despite asserting that a person of ordinary skill in the art would understand the meaning of the disputed terms and would understand that the terms provided reasonable certainty as to the scope of the claims, Chugai does not describe whom it views as a person of ordinary skill in the art. Alexion offers that, around 2008 to 2009, a person of ordinary skill in the art would have an advanced degree in a relevant field of study, including immunology, biochemistry, molecular biology, or cell biology. Parren Decl. ¶ 19. The advanced degree would likely be a doctorate level degree (or equivalent degree through training). This person would have additional experience in the research, design, and development of antibodies or characterization of protein-to-protein interaction, in particular antibody-antigen interaction. *Id*. This experience would encompass 3 to 5 years in an academic research laboratory or in the biotechnology or pharmaceutical industry. *Id*.

III. CHUGAI'S RESPONSE TO ALEXION'S BACKGROUND OF THE TECHNOLOGY AND THE '377 PATENT

Alexion's Background section contains several misleading or inaccurate statements that Chugai will briefly address in this section.[6] Alexion attributes the statement "[t]he immune system will generally produce millions of antibodies in response to each antigen" to Chugai and to Dr. Williams, and later contends that "[a]s Chugai's expert stated in his declaration, there are likely millions of unique antibodies to each antigen." (*Supra* at 7, 13). This is incorrect. Dr.

[6] Chugai does not provide an exhaustive critique of Alexion's Background section herein but reserves the right to address other statements by Alexion that are not addressed here.

Williams stated that "[i]t is the variability in CDRs that result in millions of unique antibodies, including many that have been or will be engineered to facilitate the treatment of disease." (Williams Decl. ¶ 15.) That statement means that millions of unique antibodies exist as a general matter, including many that are suitable for therapeutic use and many that are not. (Williams Reply Decl. ¶ 2.) It does not mean that there are millions of unique antibodies produced *in response to each antigen*, which is factually incorrect. (*Id*.)

Alexion states that "any change to the amino acid sequence of the variable region, especially in the CDRs, will almost invariably alter the function of the antibody." (*Supra* at 8.) This statement is incorrect as it relates to antigen binding. (Williams Reply Decl. ¶ 3.) Certain changes to the amino acid sequence of the variable region will have little or no impact on antigen binding. (*Id.*) In addition, Alexion contends that "it is unknown a priori whether a modification [to the amino acid sequence of a CDR] will increase, decrease, or not affect binding to the antigen of interest," which is also inaccurate. (*Supra* at 11.) There are many modifications whose effects are entirely or partially predictable in advance. (Williams Reply Decl. ¶ 3.) For example, in light of the '377 patent and other references, it is now known that an antibody can be conferred with a pH-dependent binding activity by substituting histidine for amino acids in the antibody, (*id.*), a fact that Alexion itself acknowledges. (*Supra* at 11.)

Chugai also takes issue with Alexion's graphical depiction of four antibody types, which is oversimplified, particularly the depiction of the "humanized antibody." (*Supra* at 10.) While the "humanized antibody" shown by Alexion is one example of an antibody that is humanized, there are many other kinds of antibodies that are also considered humanized, including those that do not have the fully human constant region shown in Alexion's example. (Williams Reply Decl. ¶ 4.) Such antibodies include those with inserted amino acid substitutions in the constant

region, as Alexion itself acknowledges, (*Infra*, at 75), among others. (Williams Reply Decl. ¶ 4.)

IV. ALEXION'S SURREPLY: CHUGAI'S QUIBBLES OVER SEMANTICS WITH THE BACKGROUND OF THE TECHNOLOGY ARE IRRELEVANT TO CLAIM CONSTRUCTION

Chugai and Dr. Williams err when they suggest that Alexion's Background section contains misleading or inaccurate statements. As shown in Dr. Parren's Sur-Reply Declaration ("Parren Sur-Reply") at ¶¶ 2-5, Alexion's description of the technology is correct.[7] Chugai's quibbles are not pertinent to the claim construction disputes, so Alexion will not explain here their inaccuracies.

Alexion's construction for "KD for the antigen" as the "monovalent equilibrium dissociation constant of an antibody to its antigen" does not seek to narrow the meaning—it applies the plain and ordinary meaning. In its Reply, Chugai neither addresses whether a POSITA understands KD as an equilibrium constant nor shows that KD encompasses the separate and distinct term "apparent KD."

With respect to "equilibrium," Chugai argues that surface plasmon resonance (SPR) can be used to determine KD without antigen binding achieving equilibrium. But Chugai ignores that SPR allows for the measurement of an accurate ka and kd in non-equilibrium conditions and that these measurements are used to provide information about the binding of the antibody and antigen at equilibrium. At bottom, if the system is configured and tested correctly, then the constant calculated is an equilibrium constant.

The Court should reject Chugai's attempt to rewrite the claim to add the language "or apparent KD." The patent disclosure describes different testing to measure KD versus apparent

[7] For example, the patent specification shows that a POSITA cannot predict the effect of a modification to the amino acid sequence. '377 patent, 58:60-59:3; Parren Sur-Reply Decl. ¶ 5.

KD, and that testing provides different information. Implementing the testing configuration for KD provides a measurement of a monovalent binding event—it assesses the affinity between an antibody and antigen. By comparison, the testing configuration for apparent KD is affected by both monovalent and divalent binding—it assesses the avidity between an antibody and an antigen. A POSITA would understand the terms KD and apparent KD as different measurements and concepts, and the intrinsic record confirms that distinction. The Court should reject Chugai's invitation to rewrite the claims to add "or apparent KD."

Despite multiple opportunities, Chugai refuses to state whether its "plain and ordinary meaning" for "dissociates from the bound antigen under conditions present in an endosome in vivo" encompasses Alexion's construction. Instead of providing insight as to whether a single antigen dissociating from an antibody-antigen complex under the conditions present in the endosome *in vivo* means that the antigen dissociates from the antibody as required by the claim term, Chugai asks the Court to hold that a separate and distinct claim limitation defines the disputed term. Chugai asserts that a POSITA need not review the limitation recited in paragraph (c) of claim 1 to understand if all the limitations of the claim are met, because whether the claimed dissociation occurs is dictated by whether the antibody exhibits the KD ratio contained in paragraph (b) of the claim. But the Federal Circuit has repeatedly cautioned against adopting constructions that render other terms superfluous.

Chugai's position concerning humanized IgG is also unavailing because a POSITA would consider the construct of the constant region of the antibody before identifying an antibody as human or humanized. The constant region ***is*** relevant to the determination.

V. DISPUTED CONSTRUCTIONS

A. "KD for the antigen" (claims 1, 8, and 9)

Chugai's Construction	Alexion's Construction
Plain and ordinary meaning. If construction of this phrase is necessary, it should be construed to mean "the antibody's KD value for the antigen to which it binds."	"Monovalent equilibrium dissociation constant of an antibody to its antigen"

1. Plaintiff's Opening Position

a. Chugai's Construction is Faithful to the Intrinsic Evidence

A person of ordinary skill in the art would understand the plain and ordinary meaning of "KD for the antigen," as it is written in claim 1, without the need for additional construction. (Williams Decl. ¶ 20); *see Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (claim terms "are generally given their ordinary and customary meaning"). To the extent the plain and ordinary meaning of this term must be expressly defined, it should be construed to mean "the antibody's KD value for the antigen to which it binds." That is the meaning that a person having ordinary skill in the art would give to this claim term in the context of the '377 patent. (Williams Decl. ¶ 20); *see Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1363 (Fed. Cir. 2016) ("The only meaning that matters in claim construction is the meaning in the context of the patent.").

Chugai's proposed construction is supported by the claim language and the specification of the '377 patent. The full context of "KD for the antigen" in the claim language is as follows:

> providing an antibody that binds to the antigen through the antigen-binding domain of the antibody and has a KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 2 to 10,000

(Ex. A, claim 1.) Based on this language, it cannot be disputed that the claim requires an antibody to bind to an antigen and that "KD" refers to the KD value of the antibody with respect

to that antigen ("an antibody that binds to the antigen…and has a KD(pH5.8)/KD(pH7.4) value"). Thus, "KD for the antigen" plainly means "the antibody's KD value for the antigen to which it binds." *See DSW, Inc. v. Shoe Pavilion, Inc.*, 537 F.3d 1342, 1347 (Fed. Cir. 2008) ("[A]bsent contravening evidence from the specification or prosecution history, plain and unambiguous claim language controls the construction analysis") (internal citations omitted).

The specification provides additional support for this construction. The specification makes clear that KD is a measure of antigen-binding activity:

> In the present invention, the difference in the antigen-binding activity between acidic and neutral pHs is not particularly limited as long as the antigen-binding activity at acidic pH is lower than that at neutral pH. However, the value of KD(pH5.8)/KD(pH7.4), which is a ratio of dissociation constant (KD) against an antigen at pH 5.8 and that at pH 7.4, is preferably 2 or greater, more preferably 10 or greater, and still more preferably 40 or greater.

('377 patent, col. 12:6-13.) The phrase "(KD) against an antigen" in the above passage can only mean the KD *of the antigen-binding molecule* against the antigen to which it binds. The antigen-binding molecule at issue in the asserted claims is an antibody, which is plainly envisioned by the specification. (*See, e.g.*, '377 patent, col. 13:4-5 ("When the antigen-binding molecule is an antibody").) Therefore, the plain and ordinary meaning of "KD for the antigen," in the context of the intrinsic evidence, is "the antibody's KD value for the antigen to which it binds."

b. Alexion's Construction Is Not Supported by the Intrinsic Evidence

Alexion's construction is not faithful to the intrinsic evidence, as understood by a person having ordinary skill in the art. Alexion seeks to introduce a narrowing limitation, "monovalent," that is not supported by the claims or specification and a second limitation, "equilibrium," that is unnecessary.

The term "monovalent" in the context of antibody-antigen binding generally refers to binding on only one of the two arms of the antibody. (Williams Decl. ¶ 21.) That is, one arm of

the antibody binds to an antigen, while the other arm remains unbound to any antigen. (*Id.*) In contrast, "divalent" binding generally means that each arm of the antibody is separately bound to its own antigen. (*Id.*) The asserted claims of the '377 patent do not limit KD to monovalent or divalent binding, and the claims therefore cover both types of binding. *See InterDigital Communs., LLC v. ITC*, 690 F.3d 1318, 1324 (Fed. Cir. 2012) ("[B]y its plain language the term 'code' is broad enough to cover both a spreading code and a non-spreading code."). Nor does the specification or prosecution history demonstrate any intent by the patentees to limit the claims to monovalent binding. *See id.* ("The plain meaning of claim language ordinarily controls unless the patentee acts as his own lexicographer and provides a special definition for a particular claim term or the patentee disavows the ordinary scope of a claim term either in the specification or during prosecution." (citing *Phillips*, 415 F.3d at 1316)).

In fact, the intrinsic evidence reveals that the KD of claim 1 includes divalent binding. According to the specification, "[i]n general, it is known that while IgG molecules monovalently bind to a soluble antigen (affinity), they divalently bind to membrane antigens (avidity)." ('377 patent, col. 67:22-25.) Claim 1 undeniably includes both soluble and membrane antigens, because claim 4 ("[t]he method of claim 1, wherein the antigen is a soluble antigen") and claim 5 ("[t]he method of claim 1, wherein the antigen is membrane-bound") both depend from claim 1. *See Trs. of Columbia Univ.*, 811 F.3d at 1370 (improper to construe an independent claim to exclude material covered by its dependent claims); *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.*, 672 F.3d 1335, 1348 (Fed. Cir. 2012) (holding that an independent claim with the limitation "magnetic member" includes ferromagnetic material in addition to a magnet, in light of dependent claim limiting "magnetic member" to a magnet). Because the specification makes clear that membrane-bound antigens bind divalently to the antibody, the KD of claim 1 includes

divalent binding.

Further support is found in Figures 3 and 4 of the patent, which concern membrane-bound and soluble antigens, respectively. According to the patent, "FIG. 3 is a schematic diagram depicting the re-binding of IgG molecules to new antigen following dissociation from membrane-bound antigen within endosomes." ('377 patent, col. 7:48-50.)

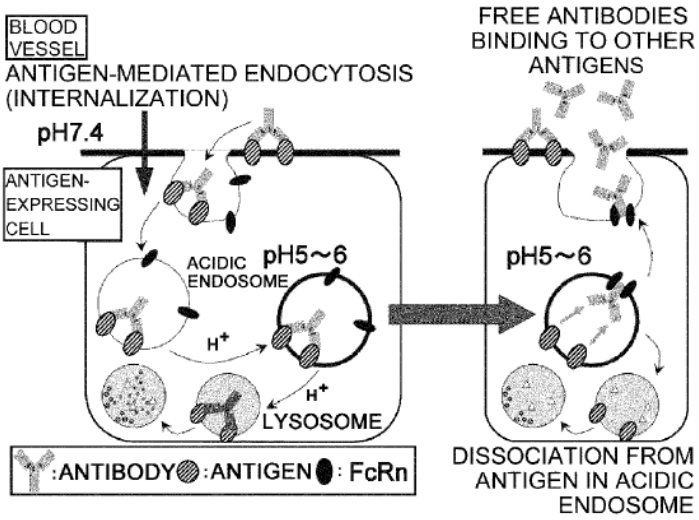


FIG. 3

Figure 3 depicts divalent binding of antigens, with one antigen for each arm of the antibody:

Divalent binding - 

Figure 4 depicts "the re-binding of IgG molecules to new antigen following dissociation from soluble antigen within endosomes." ('377 patent, col. 7:51-53.)

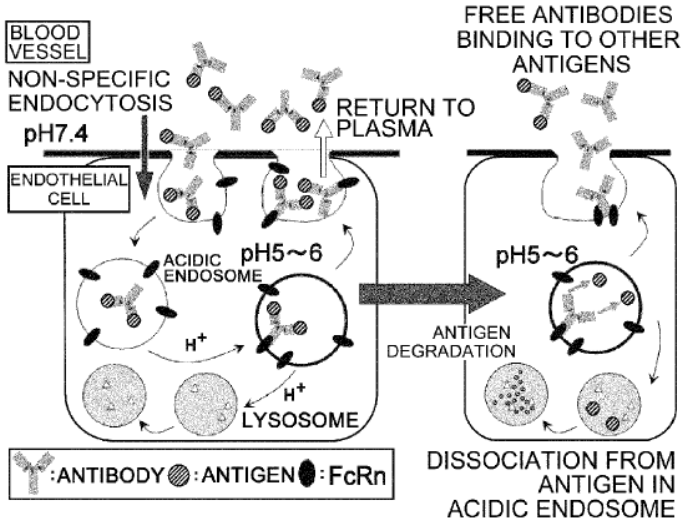


FIG. 4

Figure 4 shows some antibodies bound to an individual antigen (monovalent) and others bound to two antigens (divalent), as follows:

Monovalent -  Divalent - 

The intrinsic evidence therefore strongly supports the inclusion of both monovalent and divalent binding in the construction of "KD for the antigen." Alexion's proposal to limit the construction to monovalent binding should be rejected.

Alexion's proposal to include "equilibrium" in the construction of "KD for the antigen" is also unfounded. The word "equilibrium" does not appear in the claims and is used only once in the specification (col. 57:39), not in the context of the antibody dissociation constant. Alexion has yet to explain why it believes "equilibrium" is a necessary part of the construction, and Chugai reserves the right to further address this issue in its reply brief after Alexion has articulated its position on this claim term.

2. Defendant's Answering Position

a. The Intrinsic Record Shows that Alexion's Position is Unquestionably Correct

Alexion agrees with Chugai that a person of ordinary skill in the art would understand that the term "KD for the antigen" has a plain and accepted meaning. With that understanding, the skilled artisan would apply the definition that Alexion offers—"monovalent equilibrium dissociation constant of an antibody to its antigen." Parren Decl. ¶¶ 2, 43. Despite Chugai's protests, Alexion does not offer a narrow definition, purportedly inconsistent with the intrinsic evidence. Quite the contrary, a review of the specification compels a singular conclusion: the "KD for the antigen" refers to the ability of an antibody to bind with a single antigen under equilibrium conditions, a.k.a. the affinity of the antibody for the antigen. Parren Decl. ¶ 44. Chugai's selective citation of certain portions of the specification cannot change this conclusion. *See*, e.g., *supra* at 19 (citing 12:6-13, but failing to address 12:17-50, which discusses four distinct measurements of antibody-antigen interaction: dissociation constant (KD); apparent dissociation constant (apparent KD); dissociation rate constant (kd)[8]; and apparent dissociation rate (apparent kd)). Parren Decl. ¶ 46.

In seeking to define the required functionality of the antibody encompassed by claims 8 and 9, the claims recite that the antibody has a particular ratio of dissociation constants (KDs) under different pH conditions. This limitation requires measuring dissociation constant (KD) values for the antigen under different pH conditions. '377 patent, 171: 21-30; Parren Decl. ¶ 45. The language is clear: the KD for the antigen is required. The language neither recites nor encompasses the other measurements that the patent describes to characterize antibody-antigen binding properties. *Id.* If the claims encompassed those measurements, they would have recited

[8] "kd" is also referenced as "k_{off}." Parren Decl. ¶ 44.

the terms apparent dissociation constant (apparent KD), dissociation rate constant (kd), or apparent dissociation rate (apparent kd). The patent indisputably identifies these terms as separate and distinct measurements. '377 patent, 12: 6-50; 37:49-57. The failure of the claims to recite these other measurements shows that the claims do not encompass those measurements.

(i) To obtain an accurate measurement, KD is measured under equilibrium

Dissociation constant (KD) and dissociation rate constant (kd) are constants that describe different concepts. Parren Decl. ¶ 47. Chugai made this point during prosecution by stating "an off rate (denoted by 'koff' or 'kd') is *different* from the equilibrium dissociation constant, typically denoted as 'KD.'" Exhibit G at 10 (emphasis in original). The difference between KD and kd is abundantly clear when considering the formula for determining the dissociation constant KD.

$$\text{Dissociation Constant (KD)} = \frac{k_d}{k_a}$$

This dissociation constant (KD) relates to the propensity of an antibody to be bound to an antigen. Parren Decl. ¶¶ 46, 47. To assess this propensity, KD relies upon the association rate constant ka[9] (the rate at which an antigen will bind to an antibody) and the dissociation rate constant kd (the rate at which an antigen bound to an antibody will separate from the antibody). '377 patent, 76:48-55; Parren Decl. ¶ 47. The dissociation constant (KD) provides a numerical indicator for the binding affinity between an antibody and antigen by dividing dissociation rate constant (kd) by the association rate constant (ka). See Ex. G at 10 ("KD is defined as the value obtained by dividing the **off rate**, 'koff' (dissociation rate), by the **on rate** (association

[9] This is often referred to as "k_{on}."

rate) denoted by 'kon' or 'ka'."); *see also*, '377 patent, Tables 5, 9, 14, 16, 17 (each calculating the KD by dividing kd/ka)[10]; Parren Decl. ¶ 48. A high kd divided by a low ka results in a high KD, which indicates weaker binding (i.e., lower affinity) between the antibody and antigen. Parren Decl. ¶ 49. Conversely, a low kd divided by a high ka results in a low KD, which indicates stronger binding (i.e., higher affinity) between an antibody and an antigen. *Id*.

To determine a dissociation constant (KD), it is necessary to allow the association and dissociation of the antibodies and antigens to achieve a state of equilibrium at a range of concentrations and then determine the binding level achieved. Parren Decl. ¶ 50; *see also* Ex. 3 to Parren Decl. at 126-127. If equilibrium is not achieved, the measurement of the binding level achieved will be erroneous and thus the KD obtained will be incorrect. Parren Decl. ¶ 50. Although Chugai questions Alexion's inclusion of equilibrium in the definition of "KD for the antigen," it has not challenged that a dissociation constant (KD) is understood to be measured at equilibrium.[11] Tellingly, Chugai's expert is silent on this issue. Williams Decl. ¶¶ 20-21. Had Dr. Williams thought that a person of ordinary skill in the art would understand that the ordinary meaning of "KD for the antigen" does not require measurement at equilibrium, he could have so stated in his declaration. His failure to do so supports inclusion of "equilibrium" in the construction of "KD for the antigen." Parren Decl. ¶ 51.

[10] Table 5 provides a KD for H3pI/L73 as 1.4×10^{-9} M. This KD results from dividing 7.4×10^{-4} (1/s) by 5.4×10^{5} (1/Ms). (0.00074)/(540,000)=0.00000000137 or 1.4×10^{-9} M.

[11] In an opposition proceeding in Europe against a Chugai patent from a different family, Chugai defines KD as "being the equilibrium dissociation constant." Exhibit E to the Joint Claim Construction Brief, Opposition against EP 2552955 submission dated September 6, 2019 at 8; *see also* 21 (distinguishing between "off rates (k_d) as opposed to equilibrium dissociation constants (K_D)."). This is consistent with the statement made in the prosecution history of the '377 patent. Ex. G at 10 (describing KD as the "equilibrium dissociation constant.").

(ii) "KD for the antigen" assesses monovalent binding

Chugai's attempt to broaden the meaning of "KD for the antigen" to encompass "apparent KD for the antigen" suffers similar deficiencies. Chugai's misguided attempt rests on an argument that the specification shows that an antibody has two binding regions, which allows an antibody to bind with a single antigen (monovalent binding) or two antigens (divalent binding). But this truism does not dictate that the term "KD for the antigen" encompass the separate and distinct term "apparent KD for the antigen." A review of the full intrinsic record leads to the inescapable conclusion that "KD of the antigen" measures the monovalent binding of an antibody to an antigen at equilibrium. Parren Decl. ¶ 52.

KD and apparent KD provide different information because they use different testing configurations. Parren Decl. ¶ 53. The patent describes two separate *in-vitro* testing configurations to assess antibody-antigen binding. '377 patent, 11:65-12:5. The first configuration requires attaching antibodies to a test chip and flowing antigen as the analyte over the antibodies bound to the test chip. *Id.*, 11:65-12:1. Because each antigen has one binding site for the antibody, any antigen that adheres to an antibody bound on the chip must bind through monovalent binding. Parren Decl. ¶ 53. The patent teaches use of this configuration to test binding of soluble antigens to antibodies and the asserted claims expressly recite use of this configuration to determine the KD for the antigen. '377 patent, 11:65-12:1, 171:18-36 (see claim 1). The second configuration requires attaching the antigen to the chip and flowing antibodies as the analyte over the antigens bound to the test chip. *Id.*, 12:1-12:5. Because each antibody has two potential binding sites, a single antibody may become bound to the chip by binding a single antigen or two antigens. Parren Decl. ¶ 53. The patent teaches using this configuration to test binding of membrane-bound antigens to antibodies. '377 patent, 11:65-

12:1. The patent describes the measurement achieved by the first method, which determines monovalent binding, as the "dissociation constant (KD);" it describes the second method, which encompasses monovalent and divalent binding, as "apparent dissociation constant (apparent KD)." *Id*., 12:17-26; Parren Decl. ¶ 53.

The intrinsic record does not stop here in its distinction between measurements limited to monovalent binding versus measurements that encompass divalent binding. *See* '377 patent, 58:31-35; 67:22-26; 70:26-31. The patent repeatedly defines the former binding measurement as "affinity" and the latter binding measurement as "avidity." *Id*., 67:22-26 (antibodies "monovalently bind to a soluble antigen (affinity)" and "divalently bind to membrane antigen (avidity).") The patent defines the measurement of "affinity" as measurement of a binding constant or dissociation constant (KD) and defines measurement of "avidity" as measurement of an apparent binding constant or apparent dissociation constant.[12] *Id*., 58:31-35; Parren Decl. ¶ 54. Putting any doubt to rest, the specification also repeatedly equates affinity with dissociation constant (KD). *Id*., 74:15:1-21, (explaining that Table 7 shows "dissociation constants (affinity, KD value)" for various antibodies), 76:56-77:5 (same but discussing Table 9), 79:1-20 (same but discussing Table 11); *see also* 65:43-61 (describing the KD ratio as an affinity ratio), 83:1-17 (describing KD(pH 5.5)/KD(pH 7.4) as a ratio of affinity at pH 5.5 and pH 7.4), 84:47-66 (same), 86:23-27 ("The ratio of affinity (KD) at pH 5.8 and pH 7.4 for each antibody was calculated. The KD ratio . . . ."), 86:35-36 ("the affinity (KD) of these antibodies"). At bottom, a person of ordinary skill in the art would recognize that the intrinsic record dictates that the term

[12] Binding constant and dissociation constant (KD) are reciprocals of each other. KD=1/(Binding Constant) and Binding Constant=1/KD. Parren Decl. ¶ 54; Exhibit 4 to Parren Decl., Binding and Kinetics for Molecular Biologists, at 20 defining Dissociation Constant (KD) and binding constant (KB).

"KD for the antigen" references the monovalent binding of an antibody and an antigen, i.e., its affinity, while "apparent KD for an antigen" references a measurement that includes divalent binding between an antibody and antigen, i.e., its avidity. Parren Decl. ¶¶ 54, 55.

As with Chugai's arguments against the inclusion of "equilibrium" within the claim construction of "KD for the antigen," Dr. Williams's failure to conclude that a person of ordinary skill in the art would understand the "KD for the antigen" to include monovalent and divalent binding measurement speaks volumes. Williams Decl. ¶¶ 20-21. Instead, Dr. Williams states that an antibody may bind to a single antigen (monovalent binding) or may bind two antigens (divalent binding) and states that the patent specification discloses both. Williams Decl. ¶ 21. Not surprisingly, he does not assert that a person of ordinary skill in the art would interpret "KD for the antigen" as encompassing the measurement of affinity and avidity because that would fly in the face of the knowledge of the skilled artisan and the repeated teachings of the specification. Parren Decl. ¶¶ 52, 56. Chugai reserves that argument for its attorneys to make. But attorney argument divorced from the intrinsic record cannot support a claim construction position. *See, e.g.*, *Sound View Innovations LLC v. Facebook, Inc.*, No. 16-cv-116 (RGA), 2017 WL 2221177, at *11 (D. Del. May 19, 2017) ("Defendant also asserts that 'an off-the-shelf server cannot perform the detailed operations in the claim without additional programming.' (D.I. 82 at 101). I reject this argument. Defendant fails to cite a single source to support it. Attorney argument alone is an insufficient basis to make a technical ruling in a claim construction"); *see also, Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043 (Fed. Cir. 2017) (discounting attorney argument unsupported by evidence).

3. Plaintiff's Reply Position

a. Alexion's proposed constructions ignore the context of the invention and the plain meaning of the claims

(i) "KD for the antigen" (claims 1, 8, and 9)

Alexion's proposed construction of "KD for the antigen" represents an improper narrowing of the claim term, with proposed limitations that do not reflect the claimed invention and that are not supported by the intrinsic evidence. Alexion has failed to demonstrate that the construction should deviate from the plain and ordinary meaning of this claim term proposed by Chugai: "the antibody's KD value for the antigen to which it binds."

(1) Alexion's Proposal to Limit the Claims to "Equilibrium" KD Should Be Rejected

Alexion states that to determine KD, "it is necessary to allow the association and dissociation of the antibodies and antigens to achieve a state of equilibrium at a range of concentrations and then determine the binding level achieved." (*Supra*, at 25.) While achieving a state of equilibrium may facilitate the calculation, a state of equilibrium is not required to calculate KD, and the claims do not require it. (Williams Reply Decl. ¶ 5.) That is because KD is calculated from the Kon and Koff curves generated from the SPR experiment, and specifically, from mathematically fitting those curves accurately. (*Id.*) Accurate fitting of the Kon and Koff curves can generate an accurate KD value even if equilibrium is not achieved. (*Id.*) Thus, while the claims encompass the determination of KD from SPR experiments that reached equilibrium conditions, there is nothing in the claims or specification that requires "KD for the antigen" to be determined *only* from experiments that reached equilibrium.

Alexion's citation to a lone statement in the prosecution history does not change this conclusion. (*Supra* at 24.) That statement reads as follows: "While Lasters does provide off rates (determined by Biacore) for some nanobodies in Table 4 and [0373], an off rate (denoted

by 'koff' or 'kd') is *different* from the equilibrium dissociation constant, typically denoted as 'KD.'" (Exhibit G at 10 (emphasis in original).) As is clear from this statement, the applicants were distinguishing the invention from the Lasters prior art on the basis of the difference between Koff (Lasters) and KD (the invention). The applicants did *not* make a distinction between equilibrium KD and non-equilibrium KD calculations to overcome prior art or in any way disclaim non-equilibrium KD such that the claims must now be expressly limited to "equilibrium." Alexion does not argue that the applicants' statement reflects a clear and unmistakable disclaimer of claim scope, and the lack of such a disclaimer defeats Alexion's attempt to limit the claims to KD values obtained at equilibrium. *See Comcast IP Holdings I LLC v. Sprint Communs. Co., L.P.*, 850 F.3d 1302, 1313 (Fed. Cir. 2017) ("[F]or prosecution disclaimer to attach, our precedent requires that the alleged disavowing actions or statements made during prosecution be both clear and unmistakable.") (quoting *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1325-26 (Fed. Cir. 2003)).[13]

In short, there is no basis, scientifically or as a matter of law, to limit "KD for the antigen" to "equilibrium" KD.

(2) Alexion's Proposal to Limit the Claims to "Monovalent" KD Should Be Rejected

(a) The Asserted Claims Include Monovalent and Divalent Binding

Alexion's proposal to limit "KD for the antigen" to "monovalent" KD is also unfounded.

[13] Alexion's reliance on a similar statement from a European opposition proceeding, (*Supra* at 25 n.11), is misplaced for the same reasons, and for the additional reason that statements from a foreign proceeding, particularly from a post-issuance foreign proceeding, lack probative value in claim construction. *See Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1290 (Fed. Cir. 2006) ("[S]tatements made during prosecution of foreign counterparts to the '893 patent are irrelevant to claim construction because they were made in response to patentability requirements unique to Danish and European law."). This is especially true here because the Chugai European patent cited by Alexion is not from the same family as the '377 patent-in-suit.

The term "monovalent" does not appear in the claims and is mentioned only three times in the specification, each of which supports the inclusion of both monovalent and divalent binding in the scope of the claims. The specification draws a distinction between monovalent and divalent binding primarily to make the point that antibodies bind divalently to membrane antigens:

- "In general, it is known that while IgG molecules monovalently bind to a soluble antigen (affinity), they divalently bind to membrane antigens (avidity)." ('377 patent, col. 67:22-25.)
- "[I]t was determined that in order for a single IgG molecule to neutralize multiple membrane antigens, the pH dependency of dissociation from divalent binding (avidity) is more important than the pH dependency of monovalent binding (affinity)." ('377 patent, col. 70:27-31.)
- "[O]ne humanized anti-IL-6 receptor antibody binds to one or two membrane IL-6 receptors (monovalently or divalently)." ('377 patent, col. 59:33-35.)

Claim 1 of the '377 patent, from which asserted claims 8 and 9 depend, undeniably includes both soluble and membrane antigens, because claim 4 ("[t]he method of claim 1, wherein the antigen is a soluble antigen") and claim 5 ("[t]he method of claim 1, wherein the antigen is membrane-bound") both depend from claim 1. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) ("Other claims of the patent in question, both asserted and unasserted, can also be valuable sources of enlightenment as to the meaning of a claim term."). Because membrane antigens are within the scope of the claims, so is divalent binding, which is inextricably linked to membrane antigens in the specification, as shown above. Alexion cannot get around that dispositive fact. Not surprisingly, Alexion does not even address claim 5 in its brief, because there is no argument that can exclude membrane antigens (and hence, divalent

binding) from the scope of the claims.

Moreover, a person of ordinary skill in the art would know that soluble antigens are not limited to monovalent binding and can exhibit divalent binding under certain circumstances.[14] (Williams Reply Decl. ¶ 6.) For example, if an antibody binds to two soluble antigens rather than one, divalent binding is implicated. (*Id.*) This is confirmed by Figure 4 of the patent, which shows some antibodies bound to an individual antigen (monovalent) and others bound to two antigens (divalent), as explained and depicted in Chugai's Opening Brief. Alexion does not dispute this point, calling it a "truism" that two binding regions "allow[] an antibody to bind with a single antigen (monovalent binding) or two antigens (divalent binding)." (*Supra* at 26.) So even if membrane antigens were not part of the asserted claims, which they are in view of claim 5, the claims would still include divalent binding. Simply put, the specification and figures make clear that the claims cover both monovalent and divalent binding. (*See also* '377 patent, col. 56:29-31 ("Since IgG molecules are divalent, a single IgG molecule can neutralize up to two antigen molecules when the two sites bind to the antigens.").) Thus, while Alexion has reached a "singular conclusion" that the claims only cover the ability of an antibody "to bind with a single antigen," the intrinsic evidence directly rebuts that conclusion. (*Supra* at 23.)

(b) The Asserted Claims Include Apparent KD

Alexion tries to bootstrap its false monovalent/divalent dichotomy into an even more

[14] Alexion mistakenly suggests that Chugai did not identify the qualifications of a person of ordinary skill in the art. (*Supra* at 14.) Chugai's reliance on the knowledge of a person of ordinary skill in the art is based on the opinions of its expert, Dr. Williams, who described the requisite qualifications in his opening declaration, opining that a person of ordinary skill in the field of the invention at the time of the invention would have: 1) a Ph.D. in chemistry, biochemistry, pharmacology, or a related field, with at least four years of experience in biochemical laboratory analysis, including experience with surface plasmon resonance; or 2) an M.D., with at least four years of experience treating blood diseases with antibody therapeutics. (*See* Williams Decl. ¶ 12 .)

tenuous argument that the claims must exclude "apparent KD." The specification again undercuts Alexion's position and makes clear that apparent KD is indeed included in the scope of the claims:

> When the antigen is a soluble antigen, the antigen-binding activity can be presented in terms of the dissociation constant (KD). Alternatively, **when the antigen is a membrane antigen, the antigen-binding activity can be presented in terms of the apparent dissociation constant.** The dissociation constant (KD) and apparent dissociation constant (apparent KD) can be determined by methods known to those skilled in the art, for example, using a Biacore™ surface plasmon resonance system (GE Healthcare), Scatchard plot, or FACS.

('377 patent, col. 12:17-26 (emphasis added.) The explicit link that the specification makes between membrane antigens, which are part of the claims, and apparent dissociation constant (apparent KD), requires that apparent KD also fall within the scope of the claims. To hold otherwise would exclude a feature present in dependent claim 5 (i.e., apparent KD) from the scope of independent claim 1, which is improper. *See Trs. of Columbia Univ. v. Symantec Corp*., 811 F.3d 1359, 1370 (Fed. Cir. 2016) (improper to construe an independent claim to exclude material covered by its dependent claims).

Inclusion of apparent KD in the claims also reflects the understanding of a person of ordinary skill in the art. (Williams Reply Decl. ¶ 7.) A person of skill in the art, reading the claims and consulting the specification, would understand that the claimed invention covers both soluble and membrane antigens and that the specification refers to the dissociation constant for soluble antigens as KD and for membrane antigens as apparent KD. (*Id.*) A person of skill would therefore conclude that the "KD for the antigen" in the claim language covers both the soluble antigen KD and the membrane antigen apparent KD. (*Id.*) A person of ordinary skill would not conclude that apparent KD is excluded because that would be inconsistent with the teachings of the specification regarding membrane antigens. (*Id.*) Moreover, a person of

ordinary skill in the art would understand that "KD" is a broad concept that covers a system-dependent dissociation event and would understand that such dissociation may reflect actual KD or apparent KD depending on how the system reaction is defined. (*Id.*) Indeed, **Alexion itself** used "KD" to indicate both KD and apparent KD in its discovery requests. (*See* Ex. B at 1 ("'KD' means the dissociation constant and **includes both the actual dissociation constant and the apparent dissociation constant**. *See, e.g.*, '377 Patent at 12:17-25.") (emphasis added).) Therefore, the fact that the specification separately lists KD and apparent KD would not lead a person of ordinary skill in the art to conclude that the KD of the claims excludes apparent KD. (Williams Reply Decl. ¶ 7.) Instead, a person of skill in the art would understand, as Alexion does, that "KD for the antigen" includes both actual and apparent KD in the context of these claims. (*Id.*)

Further corroboration comes from the statement in the specification that "[t]he dissociation constant (KD) and apparent dissociation constant (apparent KD) can be determined by methods known to those skilled in the art, for example, using a Biacore™ surface plasmon resonance system." ('377 patent, col. 12:23-26.) Because the claims expressly require KD to be determined "using a surface plasmon resonance technique," a person of ordinary skill in the art would understand that the claims require the same SPR method that the specification indicates is the proper method for both KD and apparent KD. (Williams Reply Decl. ¶ 8.) This connection between the claims and the specification regarding apparent KD would further confirm that apparent KD is part of the claims. (*Id.*) Thus, the absence of an express "apparent KD" in the claim language is an insufficient basis on which to conclude that apparent KD is not covered by the claims. *See Wi-Fi One, LLC v. Broadcom Corp.*, 887 F. 3d 1329, 1344-46 (Fed. Cir. 2018) (rejecting a proposed construction for which the claim "standing alone, provides some support,"

in favor of a construction that was, instead, "faithful to the invention disclosed in the specification"), *cert. denied*, 139 S.Ct. 826 (2019). The context of the invention and the scope of the claims, particularly the inclusion of membrane antigens, requires the inclusion of apparent KD.

Alexion also latches onto the concepts of "affinity" and "avidity" to suggest that the claims only encompass the former and not the latter, and thus do not encompass apparent KD. (*Supra* at 27.) Alexion's argument is again belied by the specification. The specification repeatedly and consistently links avidity to the divalent binding of membrane antigens. (*See, e.g.*, '377 patent, col. 67:22-25 ("In general, it is known that while IgG molecules monovalently bind to a soluble antigen (affinity), they divalently bind to membrane antigens (avidity)."); *id.* at col. 70:11-14 ("Since IgG molecules are thought to normally bind divalently to membrane-bound antigen, it is thought that anti-IL-6 receptor antibodies also bind divalently (avidity) to membrane-type IL-6 receptors."); *id.* at col. 70:27-31 ("[I]t was determined that in order for a single IgG molecule to neutralize multiple membrane antigens, the pH dependency of dissociation from divalent binding (avidity) is more important than the pH dependency of monovalent binding (affinity).").) Because the claims indisputably cover membrane-bound antigens, the claims also cover avidity. Moreover, the specification directly links avidity to apparent KD. (*See* '377 patent, col. 58:33-35 ("[T]he binding strength is typically expressed as a binding constant (affinity) or apparent binding constant (avidity)." Thus, the apparent dissociation constant, i.e., apparent KD (the reciprocal of apparent binding constant), which goes hand-in hand with avidity and divalent, membrane-antigen binding, according to the

specification, is covered by the claims.[15]

In sum, in its quest to exclude divalent binding from the scope of the claims, Alexion not only ignores the intrinsic evidence but also misrepresents the scientific concepts underlying the claimed invention. Alexion's proposed construction should be rejected. The plain and ordinary meaning of "KD for the antigen" should be adopted, namely, "the antibody's KD value for the antigen to which it binds."

4. Defendant's Sur-Reply Position

a. Alexion's construction of "KD for the antigen" is correct because it recites the plain and ordinary meaning as understood by a POSITA

(i) KD is the equilibrium dissociation constant

Departing from the plain and ordinary meaning which recognizes KD as the **equilibrium** dissociation constant, Chugai focuses on the methodology employed to obtain a KD value when using surface plasmon resonance ("SPR"). *Supra* at 29, 34. Chugai again quibbles with Alexion's position by asserting that the curve fitting associated with SPR may allow determination of a KD without requiring the association and dissociation to reach equilibrium. *Id.* This argument is a red herring because it does not address the real question. What does that curve fitting seek to model and obtain? The answer is that the curve fitting seeks to model kinetics to understand the binding when the association and dissociation have reached a state of equilibrium, because that allows a POSITA to comprehend the propensity of an antigen-antibody

[15] In any case, avidity effects are not limited to the one scenario that Alexion describes, (*Supra* at 27), where membrane antigens are immobilized on the SPR chip and antibodies are the analytes that bind to the antigens. (Williams Reply Decl. ¶ 9.) Avidity can also occur when the antibodies are immobilized on the SPR chip and membrane antigens are the analytes that bind (divalently) to the antibodies. (*Id.*) And avidity can occur when soluble dimeric or trimeric antigens (e.g., TNFα) bind to antibodies immobilized on the chip. (*Id.*) Thus, Alexion's reliance on avidity to limit the claims presents an unduly narrow view of that term and is, in any event, not supported by the specification.

to be bound. Parren Sur-Reply Decl. ¶ 6. It provides the "equilibrium dissociation constant." *Id*. ¶ 7. That is precisely how a POSITA would understand the results of an SPR configured to measure the "KD for the antigen." *Id*. ¶¶ 6, 7.

Chugai's disavowal argument is equally unavailing. Alexion cites to Chugai's statement during prosecution to confirm the plain meaning—not to depart from it. *See supra* at 24-25. Tellingly, neither Chugai nor Dr. Williams addresses the textbook cited by Alexion, which shows the understanding of a POSITA that the association and dissociation rate constants are used to determine an **equilibrium** constant. Ex. 3 to Parren Decl. at 126-127. In fact, the article that Chugai cites in its Reply describes KD as the "equilibrium binding affinities." *See* Williams Reply Decl. ¶ 3 (citing Bostrom *et al.*). A POSITA's understanding, confirmed by the intrinsic evidence, is that KD is an equilibrium dissociation constant. The Court should apply that meaning.

(ii) The Court should reject Chugai's attempt to rewrite the claims to state "KD <u>or apparent KD</u> for the antigen"

Chugai's position amounts to an invitation to ignore the specification's repeated distinctions between "KD" and "apparent KD" and the specification's multiple descriptions of KD as measuring affinity, i.e., monovalent binding, and apparent KD as measuring avidity, a measurement that encompasses monovalent and divalent binding. '377 patent, 11:65-12:1, 12:17-26, 58:31-35, 67:22-26, 70:26-31, 74:15-15 (Table 7), 77:1-2 (Table 9), 79:16-18 (Table 11), 65:43-55 (KD as obtaining affinities at pH 5.8 and pH 7.4); 83:1-17, 84:47-66, 86:23-27, 86:35-36. This is improper. The Court should hold Chugai to this distinction in the claims. *Tandon Corp. v. U.S. Intern. Trade Com'n*, 831 F.2d 1017, 1024 (Fed. Cir. 1987) citing *Autogiro Company of America v. United States*, 384 F.2d 391, 397 (Ct. Cl. 1967) ("In serving its statutory purpose, the specification aids in ascertaining the scope and meaning of the language employed

in the claims inasmuch as words must be used in the same way in both the claims and the specification.").

Chugai argues that the Court should ignore the specification's distinction between KD and apparent KD because the claims cover both soluble and membrane-bound antigens. *Supra* at 31. Alexion does not dispute that the enormous breadth of the claims seeks to cover all antibodies with the recited functionality whether that antibody binds a soluble or membrane-bound antigen. But that does not allow the Court to subsume the separate term and concept of "apparent KD" into "KD." Chugai drafted its claims to recite "KD for the antigen" and included in the claims the measurement configuration that the specification teaches for obtaining KD only, i.e., binding an antibody to the chip and flowing a monovalent binding antigen over those antibodies. Chugai chose not to recite "apparent KD for the antigen," a decision it now seems to regret.

Chugai appears to ask the Court to depart from the description repeatedly provided in the specification because it is concerned that excluding "apparent KD" from the claims as written highlights a problematic flaw in the claims. This flaw stems from the fact that the specification associates KD and the testing configuration recited in the claims with soluble antigens—not membrane-bound antigens, while the claims attempt to cover both. '377 patent, 171:21-31 claim 1, 11:65-12:1, 12:17-26. Moreover, the specification provides no teaching as to how a POSITA can obtain a KD for a membrane-bound antigen—only an apparent KD. As nothing in the specification supports including the separate term "apparent KD" in the claim language, the Court should not redraft the claims to encompass the concept. *K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1364-1365 (Fed. Cir. 1999) ("Courts do not rewrite claims; instead, we give effect to the terms chosen by the patentee"); *Autogiro Co.*, 384 F.2d 396 ("Courts can neither broaden nor

narrow claims to give the patentee something different than what he set forth.").

The depth to which Chugai will go to contradict the unambiguous distinction repeatedly described in the specification is evidenced by what can only be seen as an attempt to obfuscate. Chugai attacks Alexion's construction by suggesting that soluble antigens undergo divalent binding. *Supra* at 32. As described in the patent, a soluble antigen interaction with an antibody is through monovalent binding. '377 patent, 67:21-25, 70:326-31. When a soluble antigen is used as an analyte flowing over antibodies bound to an SPR chip, that antigen, with a single binding site—an epitope—can bind with a single arm of an antibody.[16] If it binds, the soluble antigen is retained on the chip through a single connection to a single antibody. The dynamics associated with this binding are a single association event, and when it separates it is a single dissociation event. Parren Sur-Reply Decl. ¶ 8. The association and dissociation of that antigen determined by SPR measures monovalent binding. *Id.* The fact that two different antigens may participate in separate association and dissociation events on separate arms of an antibody does not mean that SPR is measuring divalent binding. *Id.* It still only measures a single association and dissociation for each of the soluble antigen analytes. The same is not true when the antibody acts as the analyte (as the patent teaches for measuring apparent KD) because SPR cannot detect whether an antibody binds to the SPR chip by a single association event (monovalently) or two association events (bivalently). Parren Sur-Reply Decl. ¶ 9. A single antibody may be bound to one or two of the membrane-bound antigens adhered to the chip. *Id.* SPR cannot identify

[16] Without reference to or support from the patent, Chugai and Dr. Williams provide an example in which a dimeric or trimeric soluble antigen exhibits divalent binding. *Supra* at 36, Fn. 15, Williams Reply Decl. at ¶ 9. Even if accurate, this isolated example from the extrinsic evidence cannot override the repeated explanations in the specification that align with the general understanding that an antigen tends to be bound by an antibody at a single epitope—an interaction that reflects monovalent binding. Parren Sur-Reply Decl. ¶ 8.

whether that antibody had to separate from one or two antigens before flowing out of the system. *Id*. Thus, when the antibody acts as the analyte, SPR provides a different measurement—the apparent KD or avidity—not the KD or affinity. The Court should reject Chugai's improper invitation to conflate these separate terms and measurements.

In a final attempt to save its construction, Chugai cobbles together some statements from the specification and assertions from Alexion's discovery requests to argue that Alexion agrees with Chugai's positions. Chugai's arguments based on Alexion's discovery requests are easily dispensed with because they actually support Alexion's position. Alexion's discovery requests expressly define KD to encompass actual and apparent KD because Alexion wanted to ensure that Chugai construed the requests broadly to encompass apparent KD—a measurement that the patent describes as distinct from KD. '377 patent, 12:17-25. The fact that Alexion deemed it necessary to state that its requests sought information about the two distinct measurements supports its position that stating simply "KD" does not encompass "apparent KD." Exhibit B at 1.

Moreover, Alexion's position is consistent with the paragraph that Chugai cites from the specification. *Supra* at 33. Chugai highlights the text "when the antigen is a membrane antigen, the antigen binding activity can be presented in terms of apparent dissociation constant." Tellingly, Chugai does not highlight the term "alternatively" that is used to transition from the separate and distinct description of dissociation constant. This text shows that KD and apparent KD are separate and distinct. '377 patent, 12:17-26, 37:49-56, 58:31-38. They are alternatives. This is confirmed when the patent describes separate testing configurations for determining KD as opposed to apparent KD. Notably, the claims recite only the configuration for KD. *Id*., e.g., 11:65-12:5.

At bottom, KD and apparent KD are different measurements that provide different information. Parren Sur-Reply Decl. ¶ 10. A POSITA would understand the distinction and the patent specification confirms that distinction. Parren Sur-Reply Decl. ¶¶ 11-14. This Court should not condone Chugai's attempt to rewrite its claims.

B. "dissociates from the bound antigen under conditions present in an endosome in vivo" (claims 1, 8, and 9)

Chugai's Construction	Alexion's Construction
Plain and ordinary meaning. If construction of this phrase is necessary, it should be construed to mean "the antibody dissociates from the bound antigen under conditions present in an endosome in vivo, which includes an intraendosomal pH generally in the range of 5.5 to 6.0."	Indefinite. In the alternative, the term means that "at least one antibody of any antigen-antibody complex taken up by a cell dissociates from the bound antigen under conditions present in the endosome in vivo."

1. Plaintiff's Opening Position

a. Chugai's Construction is Faithful to the Intrinsic Evidence

A person of ordinary skill in the art would understand the plain and ordinary meaning of "dissociates from the bound antigen under conditions present in an endosome in vivo," as it is written in claim 1, without the need for additional construction. (Williams Decl. ¶ 22.) The patentees gave no special definitions to any of the words in this claim term, and the plain meaning is clear from the context of the patent. To the extent the plain and ordinary meaning of this term must be expressly defined, it should be construed to mean "the antibody dissociates from the bound antigen under conditions present in an endosome in vivo, which includes an intraendosomal pH generally in the range of 5.5 to 6.0." That is the meaning that a person having ordinary skill in the art would give to this claim term in the context of the '377 patent. (*See* Williams Decl. ¶¶ 23-24); *see Trs. of Columbia Univ.*, 811 F.3d at 1363.

The disputed claim term appears in claim 1 of the patent, in the following context:

> administering the antibody to the individual, wherein the antibody binds to the antigen in plasma in vivo and dissociates from the bound antigen under conditions present in an endosome in vivo

The term "dissociates" clearly refers to the dissociation of the antibody from the bound antigen. Per the claim language, while binding of antibody to antigen takes place in blood plasma, the dissociation occurs in the endosome. A person of ordinary skill in the art would understand that an endosome is a vesicle within a cell in which material from the cellular surface is sorted and transported. (Williams Decl. ¶¶ 24-25.) The endosome in the context of claim 1 includes an endosome in an endothelial cell, which is a type of cell that forms the innermost layer of the blood vessel wall and can receive material from the blood plasma or deliver material to the blood plasma. (Williams Decl. ¶ 25; *see* '377 patent, Fig. 4.) A person of ordinary skill in the art would understand that conditions in blood plasma are different from conditions in an endosome. (*See* Williams Decl. ¶ 17.)

One such condition that is centrally important to the claimed invention is the pH. Scientists use pH as a measure of how acidic or alkaline a solution is. (Williams Decl. ¶ 17.) The pH scale usually ranges from 0 to 14; solutions with pH less than 7 are considered acidic and those above 7 are considered alkaline. (*Id.*) A person of ordinary skill in the art would understand that the pH in plasma is different from the pH in an endosome. (*Id.*; *see* '377 patent, col. 27:32-33 ("[T]he present inventors noted that the pH in the plasma was different from the pH in the endosomes.").) Specifically, and as the inventors recognized, the pH of plasma is normally 7.4 while endosomal pH is normally 5.5 to 6.0, which is more acidic than plasma pH. (Williams Decl. ¶ 23; *see* '377 patent, col. 27:42-46 ("The pH in the endosomes has been reported be generally an acidic pH of 5.5 to 6.0 …. Meanwhile, the pH in the plasma is known to be almost neutral (normally, pH 7.4).").) Recognizing the significance of this difference in

pH, the inventors "discovered that antibodies that strongly bind to antigens under plasma pH condition but that weakly bind to antigens under endosomal pH condition were superior in retention in the plasma, because one antibody molecule could bind to multiple antigens." ('377 patent, col. 27:34-38.) Thus, as a result of the acidic pH in the endosome, the inventors discovered that:

> [A]n antigen-binding molecule whose antigen-binding activity at acidic pH is weaker than the antigen-binding activity at neutral pH binds to the antigen in the plasma which have a neutral pH, is taken up into cells, and then dissociates from the antigen in the endosomes which have an acidic pH….As a result, the antigen-binding molecule can bind to antigens multiple times, and the pharmacokinetics is improved.

(*Id.* at col. 27:47-57; *see also* Ex. H, U.S. Patent Appl. No. 13/889,512, Response to Office Action, Filed Nov. 2, 2015, at 8 ("Applicant surprisingly found that, if the antigen-binding activity of an antibody is such that it strongly binds to the antigen in plasma (which has a neutral pH), but dissociates from the antigen in endosomes (which have a relatively acidic pH), that antibody would release its bound antigen within an endosome and then cycle (without the antigen) back to the cell surface, to be released into the plasma where it is free to bind another molecule of antigen.").)

The endosomal pH is therefore central to the understanding of the claimed invention, and the claim language "*conditions* present in an endosome in vivo" would be understood by a person of ordinary skill in the art to include *the pH conditions*, and specifically, "an intraendosomal pH generally in the range of 5.5 to 6.0." (Williams Decl. ¶ 23; *see* '377 patent, col. 27:42-44 ("The pH in the endosomes has been reported be generally an acidic pH of 5.5 to 6.0.").) Other "conditions" present in an endosome in vivo are less pertinent to the claimed invention and need not be specified in the construction of this claim term. Given the nature of an endosome, including its structure, its location within eukaryotic cells, and the functions it

provides, a person of ordinary skill would understand the kinds of conditions that would or would not be present in an endosome in vivo, and there is therefore no need for further elucidation of this term in the context of the patent. (Williams Decl. ¶ 23.)

For example, during the prosecution of the '377 patent, the examiner argued that the claimed invention was obvious in light of the prior art Ejima reference in combination with other references. (Exhibit H, U.S. Patent Appl. No. 13/88,512, Response to Office Action, Filed Nov. 2, 2015, at 7.) The inventors overcame this rejection by explaining that the laboratory chromatography experiments conducted in Ejima, which included high concentrations of arginine and $MgCl_2$, did not reflect conditions present in an endosome in vivo, as claimed in the patent. (*Id.* at 10 ("Such conditions would likely include a pH in the range of 5.5 to 6.0…but are highly unlikely to encompass an arginine concentration anywhere near the 2 M concentration that Ejima used to elute antibodies from the antigen affinity column, or a $MgCl_2$ concentration high enough to facilitate dissociation, or anything that could be characterized as 'strong chaotropic conditions.'").) The inventors' explanation prevailed, because a person of ordinary skill in the art would understand that certain conditions are likely to be present in an endosome in vivo, while others—like high laboratory concentrations of arginine and $MgCl_2$—are not. (Williams Decl. ¶ 23.) Expressly listing or defining every such condition is neither practical nor necessary. In the context of the claimed invention, the endosomal conditions that matter are the pH conditions.

Thus, to the extent the term "dissociates from the bound antigen under conditions present in an endosome in vivo" needs construction at all, it should be construed to mean "the antibody dissociates from the bound antigen under conditions present in an endosome in vivo, which includes an intraendosomal pH generally in the range of 5.5 to 6.0."

b. The "Dissociates" Claim Term Is Not Indefinite, and Alexion's Alternative Construction Is Not Supported by the Intrinsic Evidence

Alexion contends that "dissociates from the bound antigen under conditions present in an endosome in vivo" renders the asserted claims indefinite. Alexion has not yet fully articulated its indefiniteness position, but in its Invalidity Contentions Alexion asserts that "the patent specification fails to provide any insight regarding how much dissociation is required (e.g., how much must dissociate to meet the limitation recited in the claims)" and that "the patent repeatedly describes that the dissociation in the endosome is presumed if an antibody exhibits a higher KD at acidic pH compared to neutral pH." Despite arguing that the claims are indefinite, Alexion offers the following construction: "at least one antibody of any antigen-antibody complex taken up by a cell dissociates from the bound antigen under conditions present in the endosome in vivo." Alexion's positions ignore the context of the claimed invention and are wrong.

A claim is indefinite if, "read in light of the specification delineating the patent, and the prosecution history," it "fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). Here, a person of ordinary skill in the art looking at the intrinsic evidence would understand that the claimed invention is directed to treatment methods with improved antibodies that bind to antigens in a pH-dependent manner such that the antibodies dissociate from the antigen in the acidic environment of the endosome and can then return to the bloodstream for another round of antigen binding. (Williams Decl. ¶ 25.) A person of skill would further understand that whether a given antibody drug product behaves in the pH-dependent manner required by the claims requires an assessment of a population of the antibody in question, not an assessment of a lone antibody molecule. (*Id.*) That is true for at least two reasons.

First, the claims are expressly directed to administering an antibody to a patient in need, and a person of ordinary skill in the art would understand that to mean that a therapeutic dose of the antibody is required. (Williams Decl. ¶ 26.) Even the smallest therapeutic dose of an antibody contains millions of individual antibodies, and that is the context in which a person of ordinary skill in the art would understand the claims of the '377 patent. (*Id.*) Moreover, administering an individual antibody to a patient would not only have no therapeutic effect, it would be impossible to perform with current methods of administration. (*Id.*) Second, current analytical methods cannot measure the fate of an individual antibody, particularly not in vivo, so a person of ordinary skill in the art would understand that a population of antibodies is required to determine pH dependence. (*Id.* ¶ 27.) Thus, dissociation of the antibody-antigen complex in the endosome, in the context of the claims, can only refer to dissociation of a population of antibodies in the endosome such that the dissociation constant (KD) ratio falls within the claimed ranges. (*Id.* ¶ 28.)

The specification repeatedly and unmistakably confirms this understanding, as it describes what is required to determine whether the claimed dissociation has taken place. For example, the inventors repeatedly explain that proportions and concentrations of antibodies and antigens, not individual antibodies or antigens, are the operable concepts to determine pH-dependent binding and dissociation:

> [A]n antigen is dissociated within a cell…does not necessarily mean that every antigen internalized into a cell via binding to the antigen-binding molecule is dissociated from the antigen-binding molecule within the cell. ***It is acceptable that the proportion of antigen that is dissociated from the antigen-binding molecule within a cell increases when compared to before*** impairing the antigen-binding ability of the antigen-binding molecule at acidic pH as compared to that at neutral pH.

('377 patent, col. 20:6-16 (emphasis added; internal quotation marks omitted); *see also id.* col.

21:9-17; col. 90:2-12; col. 18:1-8; col. 18:31-39; 18:50-57; Figs. 13, 14, 16, 18, 20, 22, 24, 28, 29 (depicting antibody or antigen *concentration*, not the fate of an individual antibody or antigen, to assess the effectiveness of pH-dependent binding/dissociation) and corresponding Examples.).)

> [W]hether the plasma retention time of an antigen-binding molecule in a form capable of binding to antigens after administration of the antigen-binding molecule is prolonged can be assessed by ***measuring the plasma concentration of the antigen-free antigen-binding molecule*** and determining any one of parameters for the antigen-free antigen-binding molecule, such as half-life in plasma, mean plasma retention time, and clearance in plasma. ***The concentration of the antigen-free antigen-binding molecule in plasma can be measured by methods known to those skilled in the art.***

('377 patent, col. 16:9-19 (emphasis added).) One of the methods known to those of skill in the art, and referenced in the claims, is surface plasmon resonance ("SPR"). (Williams Decl. ¶ 27.) The specification explains that SPR can be used to measure dissociation of the antibody-antigen complex and thereby assess pH dependence in accordance with the invention. (*See* '377 patent, col. 17:5-19.) A person of ordinary skill in the art would understand that SPR, does not provide measurements of individual antibodies or antigens. (Williams Decl. ¶ 27.) Rather, it provides measurements based on populations of antibodies/antigens, and that is the only kind of measurement that makes sense in the context of the '377 patent and the asserted claims. (*Id.*)

For these reasons, a person of ordinary skill would have "reasonable certainty" regarding the meaning of the "dissociates" term and thus the scope of the claimed invention. (Williams Decl. ¶ 25.) The claims are therefore not indefinite. Likewise, the claims cannot be reasonably construed to require "at least one antibody" to dissociate, as proposed by Alexion. That construction flies in the face of the context of the patent and the express teachings of the specification, as explained above. Alexion's positions must be rejected.

2. Defendant's Answering Position

a. Chugai's construction does not address the crux of the dispute and its arguments against Alexion's construction lack merit

Chugai's position avoids the crux of the dispute—what is required by the term "dissociates from the bound antigen." Chugai asserts that no definition is required or, alternatively, provides a definition that essentially parrots the claim language. The flaw in this approach is evidenced by Chugai's failure to explain whether its plain meaning encompasses Alexion's proposed construction. Instead of providing clarity on claim scope, Chugai obfuscates by raising a red herring—it inaccurately describes Alexion's position as asserting that the methods of claims 8 and 9 involve the administration of a single antibody. Williams Decl. ¶¶ 24-28. But Alexion does not dispute that the separate claim language "administering the antibody to the individual" may encompass administering a dose with more than one antibody. Parren Decl. ¶ 57. In fact, Alexion's proposed construction acknowledges that the dose administered to the patient includes more than one antibody because it states "**at least one** antibody of an antigen and antibody complex taken up by a cell dissociates from the bound antigen." (emphasis added). Parren Decl. ¶¶ 3, 58. This language expresses the understanding that a cell may take up more than one antibody-antigen complex. For that to happen, more than one antibody must be present in the plasma—i.e., more than one antibody was administered to the patient. The crux of the dispute and the issue that Chugai apparently wishes to avoid is, what is the level of dissociation required in order to fall within the scope of the claim language when a dose of antibodies is administered and the cells take up multiple antibody-antigen complexes? To the extent it is something other than the construction proposed by Alexion, the claim language is indefinite

because the specification provides no guidance to understand the required level of dissociation.[17]

The claim language at issue here seeks to describe properties of the antibodies that fall within the scope of the claims. The antibodies must be capable of binding to an antigen in the plasma and, upon uptake by a cell, dissociate—separate from that antigen—under the conditions present in the endosome of the cell.[18] Parren Decl. ¶ 59. Presumably, if at least one of the antibody-antigen complexes taken up by the cell separates, then the antibody can "dissociate from the bound antigen under conditions present in the endosome in vivo." *Id*. Chugai appears to disagree because it asserts that "Alexion's positions ignore the context of the claimed invention and are wrong." *Supra* at 45. But Alexion's definition is consistent with the specification. The specification repeatedly explains that "[i]n the present invention an antigen dissociated within a cell from an [antibody] does not necessarily mean that every antigen internalized into a cell via binding to [an antibody] is dissociated from the [antibody] within the cell." '377 patent, 20:5-11; 21:6-17, 18:30-39. The specification acknowledges that only a subset of antibody-antigen complexes needs to dissociate. Yet, Chugai never explains what subset is required when it asserts that Alexion's construction is wrong. Parren Decl. ¶ 59.

[17] Alexion's Preliminary Invalidity Contentions served on June 21, 2019 include additional invalidity arguments based upon 35 U.S.C. § 112(b) (formerly 35 U.S.C. § 112, second paragraph). Alexion is awaiting discovery from Chugai relevant to these arguments. Alexion maintains these arguments and reserves the right to raise them based upon information learned through the course of fact discovery and/or developed through expert discovery.

[18] This is not the only functional language in the asserted claims. The claims require antibodies that have a certain KD ratio under different pH conditions. This requires that the antibodies have different binding properties under different pH conditions. Chugai spends the bulk of its brief arguing that the only condition that matters for "conditions present in an endosome in vivo" is the pH. Chugai appears to use this argument to bring in its expert opinion that a person of skill in the art would understand that "dissociates from the bound antigen" is met if the earlier recited KD ratio limitation of the claim is met. Williams Decl. ¶ 28. As explained below, this position runs counter to Federal Circuit precedent because it makes the limitation "dissociates from the bound antigen under conditions present in an endosome" superfluous in view of the KD ratio limitation.

(i) Chugai's first argument conflates claim terms, is legally improper, and is scientifically questionable

Chugai's first attempt to provide a meaning for "dissociates from the bound antigen under conditions present in the endosome" conflates that term with the requirement that antibodies encompassed by the claims have "a KD(pH5.8)/KD(pH7.4) value of 30 [or 40] to 10,000." '377 patent, 171:57-60. Chugai and its expert argue that the "dissociation of the antibody-antigen complex in the endosome, in the context of the claims, **can only refer to dissociation** of a population of antibodies in the endosome **such that the dissociation constant (KD) ratio falls within the claim ranges.**" *Supra* at 15; Williams Decl. ¶ 28 (emphasis added). If the determination as to whether the separate and distinct claim language "dissociates from the bound antigen under conditions present in an endosome in vivo" rises or falls on whether the KD ratio recited by the claim is met, then the claim language is superfluous. Such a construction runs afoul of established Federal Circuit precedent that repeatedly admonishes against the construction of a claim that renders a claim term meaningless. *Bicon, Inc. v. The Straumann Co.*, 441 F.3d 945, 950-951 (Fed. Cir. 2006) ("Allowing a patentee to argue that . . . characteristics specifically described in a claim are merely superfluous would render the scope of the patent ambiguous, leaving examiners and the public to guess about which language the drafter deems necessary to his claimed invention and which language is merely superfluous, nonlimiting elaboration."); *HZNP Medicines LLC, v, Actavis Laboratories, Inc.*, CV2017-2149, 2019 WL 5076226 *9 (Fed. Cir. Oct. 10, 2019) ("This reading would be contrary to the well-established 'principle that claim language should not [be] treated as meaningless.'"); *Wasica Finance GmbH v, Continental Automotive System, Inc.*, 853 F.3d 1272 1288 n. 10 (Fed. Cir. 2015) ("It is highly disfavored to construe terms in a way that renders them void, meaningless, or superfluous."); *Mformation Techs., Inc. v. Research in Motion Ltd.*, 764 F.3d 1392, 1399 (Fed. Cir. 2014)

(favoring a construction that does not render another limitation "superfluous"); *see also Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 395 F,3d 1364, 1372 (Fed. Cir. 2005).

In addition to being legally untenable, this argument is scientifically questionable. Using the KD ratio as a proxy for dissociation is problematic because two antibodies having drastically different dissociation-related *in-vivo* properties can have the same KD (the determinant of KD ratio). This is because the KD of an antibody is the dissociation rate constant (kd) divided by the association rate constant (ka). Parren Decl. ¶ 60; *see also* '377 patent, 66:4-18, Table 5 (KD shown as the quotient of kd/ka). Another review of the formula is helpful:

$$\text{Dissociation Constant (KD)} = \frac{k_d}{k_a}$$

An antibody-antigen complex that dissociates quickly (i.e., has a high kd) can have the same dissociation constant (KD) as another antibody-antigen complex that dissociates slowly (i.e., has a low kd), because the first complex may associate quickly (i.e., has a high ka) and the second complex may associate slowly (i.e., has a low ka). Parren Decl. ¶ 61. The specification does not address this issue. Instead, it discusses dissociation constant (KD) in the context of the dissociation constant (KD) ratio and discloses that the assessment requires only determining that the dissociation constant (KD) ratio falls within a set range. *Id.* This further exacerbates the problem: two different antibody-antigen complexes can have the same dissociation constant (KD) ratio despite having drastically different dissociation constants (KDs) under different pH conditions because the dissociation constant (KD) ratio is the quotient of dissociation constants (KDs) measured under different pH conditions. *Id.*

$$\text{KD ratio} = \frac{\text{KD pH 5.8}}{\text{KD pH 7.4}}$$

This shows that the KD ratio provides limited insight into dissociation within the endosome because antibodies with fast as well as slow dissociation rates (kd) can fall within the ratio range

described in the specification and included in the claims. Parren Decl. ¶ 62. The potential for antibodies with the same KD ratios to behave very differently *in vivo* would cause a person of ordinary skill in the art to wonder whether a KD ratio provides any insight into whether an antibody "dissociates from bound antigen under conditions present in an endosome in vivo" in the manner required to achieve the method of removing antigen from plasma. *Id.*

Notably, close examination of the specification supports the conclusion that using the KD ratio as a proxy for dissociation of the antibody-antigen complex in the endosome is unreliable. Example 6 of the '377 patent shows KD data for four antibodies, a parent antibody (WT), and three variants of that antibody, H3pI/L73, H170/L82 and CLH5/L73.[19] '377 patent, 65:30-66:17, Table 5. The *in-vitro* testing of Example 6 reported in Table 5 shows a KD(pH5.8)/KD(pH7.4) ratio for these variants. *Id.*, 66:4-16, Table 5 (emphasis added in

TABLE 5

Comparison of Binding of pH-Dependently Binding Clones Directed Against SR344 to Soluble IL-6 Receptor

	pH7.4			pH5.8			KD(pH5.8)/
	ka(1/Ms)	kd(1/s)	KD(M)	ka(1/Ms)	kd(1/s)	KD(M)	KD(pH7.4)
WT	5.1E+05	1.0E-03	2.1E-09	7.6E+05	3.8E-03	5.0E-09	2.4
H3pI/L73	5.4E+05	7.4E-04	1.4E-09	1.7E+05	9.7E-03	5.7E-08	41.3
H170/L82	6.8E+05	1.1E-03	1.6E-09	2.6E+04	1.7E-02	6.4E-07	393.5
CLH5/L73	7.1E+05	7.9E-04	1.1E-09	3.8E+05	2.8E-02	7.4E-08	66.1

[19] Although WT (a.k.a. PM1) is related to these three antibodies, it is not the direct parent of these antibodies. The patent shows the generation of heavy chain H53 (SEQ ID NO: 1) and light chain PF1L (SEQ ID NO: 2). These antibody chains resulted from numerous non-histidine mutations to the heavy and light chains of WT (a.k.a. PM1). Parren Decl. ¶ 37; '377 patent, 55:41-62. Compare amino acid positions 13, 16, 23, 30, 31, 43, 58, 65, 69, 70, 81, 89, 105, 107 of PM1 heavy chain (SEQ ID NO: 9) with corresponding positions in heavy chain H53 (SEQ ID NO: 1). *Id.*, cols. 89-90, 95-98. For example, position 30 of SEQ ID NO: 9 was changed from "Thr" to "Ser" and position 31 was changed from "Ser" to "Asp." *Id.* Compare positions 18, 24, 45, 51, 53, 79, 80, 83, 89, 93, 107 of PM light chain (SEQ. ID. NO: 10) with corresponding position of light chain PF1L (SEQ ID NO. 2). *Id.*, cols. 89-92, 99-100. H53 and PF1L were further mutated to generate H3pI/L73, H170/L82 and CLH5/L73. Parren Decl. ¶ 37.

highlighting below).

At 393.5, the KD ratio for H170/L82 far exceeds the ratio obtained for the other two variants. [20] If the KD ratio stands as a proxy for the ability of an antibody-antigen complex to dissociate under the conditions present in the endosome *in vivo*, one would expect H170/L82 performance *in vivo* to exceed that of H3pI/L53 and CLH5/L73.[21] Parren Decl. ¶ 63. But the patent shows the opposite. Example 8 of the patent provides *in-vivo* data of these antibodies in mice and concludes that "the effect of prolonging plasma persistence time of H170/L82 was weaker than that of H3pI/L73 and CLH5/L73." '377 patent, 70:7-11. Taken together, these data show that the KD ratio was not indicative of *in-vivo* performance. Parren Decl. ¶ 63; *see also HZNP Medicines*, 2019 WL 5076226, at *14 (finding inconsistency in test results described in specification supported a finding of indefiniteness.) This further explains why the Court should reject Chugai's attempt to conflate these limitations.

(ii) Chugai ignores whole classes of antibodies in an attempt to support its position

Chugai's second argument as to how a skilled artisan would understand the claim term in view of the specification is also flawed. Chugai asserts that several comparisons described in the specification allow a person of ordinary skill in the art to determine whether a particular antibody

[20] Table 17 of the '377 patent inexplicably reports a drastically different KD ratio of 61.9 for H170/L82. '377 patent, 85-86, Table 17. The '377 patent does not provide an explanation as to why the same antibody exhibits a 5-fold different in KD ratios.

[21] The specification suggests that the ability of an antibody-antigen complex to dissociate may be assessed by comparing whether the pharmacokinetics of a variant antibody are improved compared with the pharmacokinetics of the wild type (WT). '377 patent, 69:18-24. This comparison is only meaningful if a parent antibody exists to provide a benchmark. Parren Decl. ¶ 64. For a non-variant antibody (i.e., antibody with naturally-occurring variable region), a person of skill in the art could not determine that dissociation in the endosome results based upon the pharmacokinetics of the antibody. *Id.*

functions as the claim requires. *Supra* at 46. Chugai asserts that a skilled artisan would understand whether an antibody dissociates as required by the claim by evaluating whether the portion of the antibody that dissociates increases or whether the plasma retention time is prolonged.[22] *See Supra* at 46-47 (citing '377 patent, 20:6-16, 16:9-19). This argument fails because it is unclear what reference of comparison should be used to assess whether the portion of the antibody that dissociates increases or whether the plasma retention time is prolonged.[23] Both comparisons require a benchmark to determine whether "the proportion of antigen that is dissociated" increases or "the plasma retention time . . . is prolonged." A benchmark may exist if the antibody encompassed by the claims results from mutating an existing antibody. Parren Decl. ¶ 64. But the claims do not require the antibody to have been mutated. And where the variable region, particularly its CDRs, of a human or humanized antibody results from inoculating an animal, from a phage display, or is directly obtained from a human cell, a parent antibody is not available to determine that the "the portion of antigen that is dissociated" increases or "the plasma retention time . . . is prolonged." Parren Decl. ¶ 66.

Chugai seeks to distract attention from this issue by repeatedly describing the method of

[22] Tellingly, Chugai does not cite to Dr. Williams's declaration to support the argument that these comparisons would allow a person of ordinary skill in the art to understand the level of dissociation required by the claim. Instead, Chugai cites to Dr. Williams's statements that SPR, an *in-vitro* test for determining KD and not a method pertinent to the comparisons discussed in '377 patent, 20:6-16 or 16:9-19, provides measurements related to a collection of antibodies as opposed to a single antibody. Parren Decl. ¶ 64. This is a non sequitur.

[23] Chugai cites to Figures 13, 14, 16, 18, 20, 22, 24, 28, and 29 for the proposition that the claim encompasses administration of a number of antibodies as opposed to a single antibody. *Supra* at 46-47. This is an issue Alexion never disputed. Chugai does not assert that these figures allow a skilled artisan to understand the dissociation required by the claims. Many of these figures suffer the same deficiency as the excerpted patent text because they require a comparison with a parent antibody. *See* '377 patent, Figures 13, 14, 16, 18, 20 (referencing a WT). Moreover, Chugai does not explain how these figures show a relationship between the pH-dependent binding properties of the antibodies and the claim requirement that the antibody-antigen complex dissociate under conditions present in the endosome. Parren Decl. ¶ 65.

the '377 patent as utilizing "modified antibodies" or "improved antibodies." *Supra* at 2-3 ("The '377 patent discloses methods . . . using antibodies modified . . . . The modified antibodies are capable . . . ."), 4 ("the modified antibodies taught by the claimed invention"); *see also* Williams Decl. ¶¶ 17, 18, 26 ("claimed invention is directed to treatment methods with improved antibodies"). But the asserted claims are not limited to mutated variants of an existing antibody. As such, Chugai's proposed solution to the specification's failure to provide insight into the required dissociation to meet the claim limitation is inapplicable to entire classes of antibodies that claims 8 and 9 encompass. Asserted claims 8 and 9 are not limited to antibodies engineered through mutation of the variable regions **with** histidine to achieve the functional requirements of the claims. The asserted claims encompass mutated antibodies and antibodies obtained from phage display, animals, or even humans. The absence of entire classes of antibodies from Chugai's proposed solution to the claims' indefiniteness supports a conclusion that the specification fails to provide the requisite guidance.

b. Considering the nature of antibody-antigen binding, a skilled artisan would conclude that the claim language and specification fail to provide reasonable certainty as to the claim scope

Patent claims must particularly point out and distinctly claim the subject matter regarded as the invention. 35 U.S.C. § 112, ¶ 2 (pre-AIA)/ §112(b) (AIA). A claim, when viewed in light of the intrinsic evidence, must "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus Inc. v. Biosig Instruments, Inc.*, 134 S.Ct. 2120, 2129 (2014). When confronted with a claim term that suggests that some degree of activity must occur, "it is not enough . . . to identify 'some standard for measuring the scope of the phrase.'" *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370-71 (Fed. Cir. 2014). The claims, when read in light of the specification and the prosecution history, must provide objective

boundaries for those skilled in the art. *See Nautilus*, 134 S.Ct. at 2130 and n. 8 (indicating that there is an indefiniteness problem if the claim language "might mean several different things and 'no informed and confident choice is available among the contending definitions'").

As discussed above, the specification repeatedly explains that "[i]n the present invention an antigen dissociated within a cell from an [antibody] does not necessarily mean that every antigen internalized into a cell via binding to [an antibody] is dissociated from the [antibody] within the cell." '377 patent, 20:5-11; 21:6-17, 18:30-39. While the specification acknowledges that only a subset needs to dissociate, neither the claims nor the specification explains the subset required to meet the dissociation limitation in the claims. The absence of a meaningful parameter to judge dissociation presents uncertainty as to claim scope because even antibodies that do not bind in a pH-dependent manner are likely to exhibit dissociation in the endosome. Parren Decl. ¶ 67. This occurs because antibody-antigen binding is a dynamic process in which antibodies and antigens will repeatedly bind and separate. *Id*. The dynamic nature of the process is shown by the formula:

$$A + B \underset{kd}{\overset{ka}{\rightleftharpoons}} AB$$

All antibody and antigen complexes have a dissociation constant (KD) and a dissociation rate constant (kd) under all conditions, i.e., all antibody-antigen complexes will experience some level of dissociation. With this knowledge, a person of ordinary skill in the art would expect the specification to provide insight into the level of dissociation in an endosome that shows that an antibody practices the dissociation limitation required by the claims. *Id* . But the patent specification fails to provide guidance as to the necessary level. *See, e.g.*, *Icon Health & Fitness, Inc. v. Polar Electro Oy*, 656 Fed. Appx. 1008, 1015 (Fed. Cir. 2016) (finding that the district

court did not err by relying on expert testimony to conclude that disputed claim terms were relative terms that had meaning only in the context of a defined reference and were therefore indefinite).

While the specification discusses calculating a dissociation rate constant (kd) under different pH conditions, it does not provide insight into a dissociation rate constant (kd) that shows that an antibody "dissociates from the bound antigen under conditions present in the endosome in vivo" in the manner required by the claims. Parren Decl. ¶¶ 2, 68. Considering that the asserted claims purport to encompass any antibody that binds to any antigen, it is not surprising that the patent specification does not describe a dissociation rate constant (kd) that will ensure that the antibody exhibits the claimed property. Parren Decl. ¶ 68. The patent specification appears to suggest that any antibody that achieves a certain dissociation constant (KD) ratio or dissociation rate constant (kd) ratio will act *in vivo* in a way that the patent purports will achieve the methods claimed. *Id*. But this is not the case because an antibody that exhibits the ratios discussed in the specification may have a dissociation rate constant (kd) that does not allow for dissociation in the endosome as recited in the claims. *Id*. Simply because an antibody has a dissociation constant (KD) ratio suggesting that an antibody exhibits pH-dependent binding does not mean that the antibody exhibits a dissociation rate constant (kd) at acidic pH necessary to practice the claimed method. *Id*. The dissociation constant (KD) ratio is a function of the association rate constant (ka) and dissociation rate constant (kd) determined for an antibody-antigen complex under different pH conditions.[24] *Id*. Depending on those constants at plasma and endosomal pH, the ratio may be satisfied while the dissociation rate constant (kd) at

[24] An antibody-antigen complex will have an association rate constant (ka) and dissociation rate constant (kd) under the conditions of the endosome. These rates will affect whether an antibody exists in the endosome in a state where it is free of antigen. Parren Decl. ¶ 69.

endosomal pH is inadequate to show that the antibody "dissociates from the bound antigen" in a manner that practices the claimed method. *Id*. Similarly, the patent states that the dissociation rate constant (kd) ratio may suggest that an antibody exhibits pH-dependent binding. But if the dissociation rate constant is low under both plasma and acidic conditions, then the dissociation rate constant (kd) under endosomal pH conditions may be at a level that does not show that the antibody "dissociates from the bound antigen under the conditions present in an endosome" in the manner recited in the claims. Parren Decl. ¶ 69. Considering that each antibody and antigen will have different association and dissociation rate constants, it is difficult to define a universal dissociation rate constant (kd) that shows that the antibody "dissociates from the bound antigen under the conditions present in an endosome in vivo." *Id*. This leaves a person of ordinary skill in the art to wonder what level of dissociation must occur under the conditions present in the endosome *in vivo*. *See,* e.g., *Interval Licensing*, 766 F.3d at 1371 (on an allegation of indefiniteness, a term of degree fails to provide sufficient notice of its scope if it depends on the unpredictable vagaries of any one person's opinion); *HZNP Medicines*, 2019 WL 5076226, at *14 (failure to provide clarity on the standard for evaluating a claim limitation supported by a finding of indefiniteness); *Bayer Intellectual Property GmbH v. Chilcott Co., LLC*, No. 12-1032-GMS, 2015 WL 1849015, at *3 (D. Del. Apr. 21, 2016) (finding claim term indefinite because the intrinsic record failed to provide a frame of reference).

The breadth of asserted claims 8 and 9—encompassing all antibodies with the claimed functional properties that bind with any antigen—makes it difficult to draft claim language that describes what must occur *in vivo* to practice the claimed method. Parren Decl. ¶ 70. As a skilled artisan starts with the understanding that all antibody-antigen complexes will associate and dissociate under all conditions over time due to the dynamic nature of antibody and antigen

binding, that artisan would look to the specification to understand the dissociation required by "dissociates from the bound antigen under conditions present in an endosome in vivo." *Id*. The specification fails to provide such a metric. *Id*. It provides no insights, particularly for antibodies with naturally-occurring variable regions. A skilled artisan could not determine whether an antibody generated from an animal or phage display, or isolated from an individual's cell, exhibits the claimed functionality. Parren Decl. ¶¶ 70, 71. Chugai's arguments do not remedy this failure. First, Chugai seeks to rewrite the claim by conflating "dissociates from the bound antigen under conditions present in the endosome in vivo" with a "KD(pH5.8)/KD(pH7.4 value of 30 (claim 8)/40 (claim 9) or higher." This is legally inappropriate and scientifically unreliable. Second, Chugai's arguments attempt to at most address only a subset of antibodies—variants that have a parent antibody that provides a benchmark. This excludes entire classes of antibodies that are purportedly covered by the asserted claims. The failure of the claim language to provide reasonable certainty as to whether entire classes of antibodies meet the claim requirement shows that claims 8 and 9 do not comply with 35 U.S.C. § 112(b). Therefore, the Court should find that the claim is invalid as indefinite.

3. Plaintiff's Reply Position

a. "Dissociates" Is Not Indefinite

Alexion contends that the "dissociates" term is indefinite but fails to grasp what the claimed invention requires. A person of ordinary skill in the art would understand that the claims require the administration of an antibody having certain properties, i.e., "an antibody that binds to the antigen through the antigen-binding domain of the antibody and has a KD(pH5.8)/KD(pH7.4) value" in the claimed ranges and is "a human IgG or a humanized IgG," wherein, following administration, the antibody binds to an antigen in plasma and dissociates from that antigen within an endosome. (Williams Reply Decl. ¶ 10.) So long as the antibody has

the claimed properties and (1) is administered; (2) binds to antigen in plasma; and (3) dissociates from the antigen in an endosome, the claim is practiced. There is no need for additional information to understand the claims with reasonable certainty, and thus the claims are not indefinite. (*Id*.) *See Nautilus, Inc. v. Biosig Instruments, Inc*., 572 U.S. 898, 901 (2014).

(i) There Is No "Level of Dissociation" Required

Alexion's indefiniteness position reflects a misunderstanding of Chugai's invention and the claim language that describes it. Alexion focuses its arguments on the "level of dissociation" required by the claims, which plainly reveals Alexion's misconception of the invention. There is no numerical "level of dissociation" required any more than there is a "level of administration" or "level of binding" required by the claims. Indeed, it is telling that Alexion argues that a person of skill would not know how much dissociation is required to practice the claims but never argues that a person of skill would have any issues understanding how much antibody must be administered or how much must bind to the antigen to practice the claims. (*See* '377 patent, claim 1 ("*administering* the antibody to the individual, wherein the antibody *binds* to the antigen in plasma in vivo and *dissociates* from the bound antigen") (emphasis added).). Alexion's lack of objection to the definiteness of the administrating and binding steps undercuts its position that the dissociating step is somehow incomprehensible to a person of ordinary skill in the art.

A person of ordinary skill in the art would understand that all antibodies in the context of the claimed invention, administered to a patient, will bind and dissociate in the plasma/endosome to some extent, due to the nature of antibody-antigen kinetics in vivo. (Williams Reply Decl. ¶ 10.) The amount of binding and dissociation is not relevant to the claimed invention. What matters under the plain language of the claims is that the antibody is administered and then binds and dissociates. Alexion itself admits that "*all* antibody-antigen complexes will associate and

dissociate under *all* conditions over time due to the dynamic nature of antibody and antigen binding." (*Supra* at 58 (emphasis added); *see also supra* at 56 ("[A]ntibody-antigen binding is a dynamic process in which antibodies and antigens will repeatedly bind and separate.").) And that is all the claim requires to practice the invention. (*See* '377 patent, col. 28:57-61 ("It is *presumed* that such an antigen-binding molecule, which weakly binds to an antigen at acidic pH, easily dissociates from the antigen under the endosomal acidic condition, and that after internalization into cells, it binds to FcRn and is easily released to the outside of the cells.") (emphasis added); *see also id.*, col. 58:23-25 ("[A]n antibody that weakly binds to an antigen at pH 5.5 to 6.0 is considered to dissociate from the antigen under intraendosomal acidic conditions.").) A numerical "level of dissociation" associated with the binding-dissociation process is not required by the claims, and a person of ordinary skill in the art would understand the dissociation that needs to occur in the context of the claims without knowing the "level of dissociation." (Williams Reply Decl. ¶ 10.)

Alexion's insistence on a numerical "level of dissociation" reflects Alexion's position that "dissociates" is a term of degree and is indefinite because the patent does not state how much dissociation must occur. Alexion's position is not well-founded. As the Federal Circuit has explained: "[W]e have rejected the proposition that claims involving terms of degree are inherently indefinite. . . Thus, a patentee need not define his invention with mathematical precision in order to comply with the definiteness requirement." *Sonix Tech. Co. v. Publ'ns Int'l, Ltd.*, 844 F.3d 1370, 1377 (Fed. Cir. 2017) (citations and quotation marks omitted). Indeed, "[c]laim language employing terms of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the context of the invention." *Biosig Instruments, Inc. v. Nautilus, Inc.*, 783 F.3d 1374, 1378 (Fed. Cir. 2015) (quotation marks and

citation omitted). Here, the claims provide sufficient context and certainty for a person of ordinary skill in the art to understand the full scope of what is required by the claims and by the "dissociates" term in particular.[25] As long as the antibody has the claimed properties and it binds and dissociates upon administration, as all antibodies do, then the claim is practiced.

(ii) It Is Proper to Consider the "Dissociates" Term in Connection With the Claimed KD Ratios

Alexion suggests that considering "dissociates" and "ratio of KD" in tandem, as Chugai proposes, would render the "dissociates" term superfluous. (*Supra* at 49-50.). Not so. The Federal Circuit has made it abundantly clear that the meaning of a claim term must be derived from the context of the claims themselves. *See Phillips*, 415 F.3d at 1314. In other words, the meaning of a claim term not only can be but *should be* determined based on the surrounding claim language. That is precisely Chugai's position regarding the meaning of "dissociates." If an antibody with the claimed properties, most importantly the KD ratio, is administered and then binds and dissociates, the claim is satisfied. Conversely, if an antibody does not have the claimed KD ratio, no amount of dissociation will bring it within the scope of the claims. Thus, whether the claimed dissociation has occurred can be understood by determining whether the KD ratio falls within the claimed ranges. As the *Philips* court explained: "This court's cases provide numerous similar examples in which the use of a term within the claim provides a firm basis for

[25] The indefiniteness cases cited by Alexion, (*Supra* at 58), involved claim terms that, unlike those here, were highly subjective in nature. *See Interval Licensing LLC v. AOL, Inc*., 766 F.3d 1364, 1371 (Fed. Cir. 2014) ("The patents' 'unobtrusive manner' phrase is highly subjective and, on its face, provides little guidance to one of skill in the art."); *HZNP Meds. LLC v. Actavis Labs. UT, Inc*., 940 F.3d 680, 696 (Fed. Cir. 2019) (finding "better drying time" indefinite); *Bayer Intellectual Prop. GmbH v. Warner Chilcott Co., LLC,* No. 12–1032, 2015 WL 1849015, *1 (D. Del. April 21, 2015) (finding that "the [claimed] words of degree—i.e., 'high,' 'low,' 'satisfactory,' and 'reliable'—had no standards against which to draw comparisons, and the patent offered no suggestions for how to measure these criteria"), *aff'd*, 645 Fed. Appx. 993 (Fed. Cir. 2016). These cases are therefore inapposite.

construing the term." *Id*. (citing *Mars, Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1374 (Fed. Cir. 2004) where "claim term 'ingredients' [was] construed in light of the use of the term 'mixture' in the same claim phrase" and *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1356 (Fed. Cir. 1999) where "claim term 'discharge rate' [was] construed in light of the use of the same term in another limitation of the same claim"). Therefore, Chugai's position that "dissociation of the antibody-antigen complex in the endosome, in the context of the claims, can only refer to dissociation of a population of antibodies in the endosome such that the dissociation constant (KD) ratio falls within the claimed ranges" (Opening at 15) is entirely consistent with the teaching of *Philips* that one claim term may inform the meaning of another. *Phillips*, 415 F.3d at 1314.

Alexion itself acknowledged the relationship between dissociates and KD ratio in its Invalidity Contentions, where it stated:

> To the extent that the claim term "dissociates . . . under the conditions present in an endosome in vivo" requires more than that the antibody exhibit different binding affinities at plasma pH compared to endosomal pH, the claims are indefinite because the patent specification fails to provide any insight regarding how much dissociation is required….

(Exhibit C, Alexion's Invalidity Contentions at 51.) Alexion has therefore already acknowledged in this litigation that there is no indefiniteness if "dissociates" means that "the antibody exhibit[s] different binding affinities at plasma pH compared to endosomal pH." The binding affinity at plasma pH compared to the binding affinity at endosomal pH *is the definition of KD ratio*. (*Supra* at 27 n.12 ("Binding constant and dissociation constant (KD) are reciprocals of each other."); Williams Reply Decl. ¶ 11.) Thus, by Alexion's own admission, if the claimed dissociation is understood to indicate that it is merely a function of the KD ratio, then the claims are not indefinite. That understanding of the claimed dissociation is precisely the explanation

proposed by Chugai.

In sum, the "level of dissociation" that Alexion so eagerly seeks is governed by the KD ratio for that antibody with respect to the antigen and the kinetic interactions, i.e., binding and dissociation, that take place as a result of that ratio. (Williams Reply Decl. ¶ 10.) Thus, the "dissociates" claim term is neither superfluous nor indefinite.

(iii) The Claims Require Specific KD Ratios, Not KD Values or ka/kd Values

Alexion next tries to muddy the waters by arguing that the same KD values can result from different underlying kd and ka values and the same KD ratio can result from different underlying KD values. (*Supra*, at 51.) While Alexion is of course correct from a mathematical standpoint, Alexion's point is unremarkable from a patent claim standpoint. It does not matter how the claimed KD ratios are achieved, whether from a high numerator and a low denominator or some other combination. What matters is whether the KD ratio falls within the scope of the claims, because that ratio will dictate whether a given antibody has the required properties to practice the claimed invention when it binds and dissociates upon administration. For this reason, from a patent claim standpoint, Alexion's argument that "the KD ratio provides limited insight into dissociation within the endosome" is wrong. (*Supra* at 51.) The KD ratio defines an essential property of the antibodies covered by the claims and because those antibodies will, by Alexion's own admission, bind and dissociate repeatedly in vivo, no further "insight" is needed to understand the meaning of "dissociate" in the context of the claims. Likewise, the claims do not require any numerical "in-vivo performance" metric by which to judge dissociation, as Alexion contends. (*Supra* at 53.) The claimed dissociation will occur if antibodies with the claimed properties are administered and then bind to antigens in plasma and dissociate from the antigens in the endosome. As explained above, such binding and dissociation occurs repeatedly

in vivo for administered antibodies, (*see also Supra* at 56 ("all antibody-antigen complexes will experience some level of dissociation"), and nothing further is needed to understand the dissociation required by the claims.[26]

(iv) Chugai's Position Does Not "Ignore[] Whole Classes of Antibodies"

Alexion's allegation that "Chugai ignores whole classes of antibodies" is baseless. (*Supra* at 53.) The antibodies covered by the claims are those that "bind[] to the antigen through the antigen-binding domain of the antibody and [have] a KD(pH5.8)/KD(pH7.4) value" within the claimed ranges. ('377 patent, claim 1.) Alexion has not identified a single antibody by name that satisfies this requirement and that Chugai "ignores." Instead, Alexion offers only theoretical conjecture from its expert about vague classes of antibodies, without ever identifying specific antibodies, much less describing how those antibodies satisfy the KD ratios required by the claims. (*Supra* at 53-55.) Alexion could have selected "antibody" as a claim term to construe if it believed a special definition was needed. But it did not do so.[27] Consequently, the antibodies

[26] Alexion states that "even antibodies that do not bind in a pH-dependent manner are likely to exhibit dissociation in the endosome." (*Supra* at 56.) Such antibodies are not covered by the claims if their KD ratios do not fall within the claimed ranges, and such antibodies are therefore not relevant to the meaning of "dissociates."

[27] Alexion's scientific analysis is misleading in any event. Alexion states that "[a] skilled artisan could not determine whether an antibody generated from an animal or phage display, or isolated from an individual's cell, exhibits the claimed functionality." (*Supra* at 59.) This is not correct. A person of ordinary skill in the art would understand that generation or isolation of such antibodies would be done for a reason, namely, to identify an improved characteristic. (Williams Reply Decl. ¶ 12.) The improvement would be a specific property, e.g., pH-dependent binding, and would be compared to an existing molecule as a reference starting point. (*Id.*) To test that property, in vitro assays, such as SPR, would be set up to determine whether a given antibody exhibits the property at the desired levels, based on a comparison with the reference molecule. (*Id.*) In other words, a person of ordinary skill in the art would understand that generation or isolation of antibodies is not performed in a vacuum; it is performed to identify a specific, improved characteristic compared to a reference molecule. (*Id.*) Thus, contrary to Alexion's assertion that "it is unclear what reference of comparison should be used," (*Supra* at 54), a person of ordinary skill in the art would select a reference of comparison based on the property it seeks to enhance and the desired levels of that enhancement. (Williams Reply Decl. ¶ 12.)

that fall within the scope of the claims are those with the required KD ratios at the specified pH values. No additional information is needed to understand the claims.

(v) Alexion Has Applied the "Dissociates" Term in This Litigation Without Any Uncertainty

Finally, Alexion's own statements in this litigation demonstrate that Alexion knows what the "dissociates" claim term means. In its Invalidity Contentions, Alexion stated that "[e]culizumab is a pH-dependent antibody that binds C5 alpha in the neutral conditions of plasma and dissociates from C5 alpha under acidic conditions in the endosome….eculizumab exhibits a KD ratio of low to high pH of at least 19….Therefore, Alexion Soliris® (eculizumab) and/or its Prescribing Information anticipate claims 1, 8, and 9." (Alexion's Invalidity Contentions at 23.) In asserting that eculizumab practices the claims, Alexion makes no mention of any "level of dissociation" or the need for such level in order to understand whether eculizumab satisfies the claims. Instead, Alexion simply asserts that eculizumab exhibits the claimed dissociation due to the "acidic conditions in the endosome" and the KD ratio that eculizumab possesses. Alexion makes similar arguments throughout its Invalidity Contentions. (*See, e.g.*, *id.* at 38 (alleging that prior art combinations render the claims obvious based on KD ratios and without any specified "level of dissociation").)

Alexion's statements further support Chugai's position that a person of ordinary skill in the art would understand the claims with reasonable certainty. Alexion's indefiniteness arguments should be rejected.

b. Chugai's Proposed Construction Reflects the Plain and Ordinary Meaning

Other than its indefiniteness position, Alexion does not take issue with any aspect of Chugai's proposed construction. That is not surprising, as Chugai's construction tracks the claim language and expands that language to indicate that the "conditions present in an endosome in

vivo" include "an intraendosomal pH generally in the range of 5.5 to 6.0." (Dkt. 41-1, Jt. Cl. Constr. Chart, at 3-4.) That intraendosomal pH range reflects the understanding of a person of ordinary skill in the art and is squarely supported by the specification. (Williams Decl. ¶ 23; *see* '377 patent, col. 27:42-44 ("The pH in the endosomes has been reported [to] be generally an acidic pH of 5.5 to 6.0.").) Thus, to the extent the "dissociates" term needs construction at all, it should be construed to mean "the antibody dissociates from the bound antigen under conditions present in an endosome in vivo, which includes an intraendosomal pH generally in the range of 5.5 to 6.0."

4. Defendant's Sur-Reply Position

a. Incapable of articulating a plain meaning that allows a POSITA to understand the requirements of "dissociates from the bound antigen under conditions present in an endosome in vivo," Chugai asks the Court to focus on the KD ratio of the claims

In its responsive claim construction brief, Alexion explained that the present claim construction dispute arose from Chugai's inability to say whether its plain and ordinary meaning encompasses Alexion's construction that at least one antibody taken up by a cell dissociates from the bound antigen. Despite Alexion presenting this question in its responsive brief, it remains unanswered. *Supra* at 48 ("The flaw in this approach is evidenced by Chugai's failure to explain whether its plain meaning encompasses Alexion's proposed construction."). Chugai sidesteps the question by noting that all administered antibodies will have some level of association and dissociation under the conditions present *in vivo* because of the kinetic nature of antigen-antibody binding, and it seeks to tie this natural phenomenon to "the claimed invention." *Supra* at 60. But this occurs for all administered antibodies, irrespective of even whether those antibodies exhibit pH-dependent binding. Parren Sur-Reply Decl. ¶ 15.

Confronted with an inability to describe what the language adds to the claim, Chugai is

forced to point to a separate and distinct limitation to determine whether a particular antibody meets the limitation "dissociates from the bound antigen under conditions present in an endosome in vivo." *Supra* at 62. While Alexion acknowledges that other claim limitations may inform the meaning of separate language in a claim, the other limitations cannot be the test by which a POSITA understands whether a separate and distinct limitation is met. Such an approach would render the claim limitation superfluous. *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950-951 (Fed. Cir. 2006); *see also* legal citations, *supra* at 50. That is precisely what Chugai suggests here. Chugai asserts that if a therapeutic antibody has the claimed KD ratio, it necessarily meets the claim limitation recited in paragraph (c) of claim 1; if it does not meet the claimed KD ratio, it does not meet paragraph (c) of claim 1. *Supra* at 62 ("Thus, whether the claimed dissociation has occurred can be understood by determining whether the KD ratio falls within the claimed ranges"); 64 (asserting that all that matters is "whether the KD ratio falls within the scope of the claims, because that ratio will dictate whether a given antibody has the required properties to practice the claimed invention when it binds and dissociates upon administration"). By articulating a position that focuses solely on an antibody achieving the KD ratio recited in limitation (b) of claim 1, Chugai effectively crosses out the language of limitation (c). That is improper.

Chugai cites to Alexion's Preliminary Invalidity Contentions to suggest that Alexion proposed defining the language in a way that renders it superfluous. This reference, however, is belied by Alexion's introductory statement in the contentions. *Supra* at 63 and 66.[28] Alexion

[28] Chugai cites to Alexion's position that administration of eculizumab anticipates claim 1 to assert that Alexion agrees that the KD ratio subsumes the latter limitation. Alexion based this position on Chugai's infringement contentions which solely rely on *in vitro* testing to assert that ravulizumab infringes the asserted claims. Because Chugai focused solely on *in vitro* testing at different pH values to assert that ravulizumab meets limitation (c) of claim 1, Alexion similarly

made clear that it was providing its preliminary contentions based upon its understanding of the claim construction offered by Chugai and stated that "[n]othing herein should be construed as setting forth the claim construction positions of Alexion." Ex. C at 1.

Under the theory that if you repeat an argument enough, it must be true, Chugai again asserts it is all about the KD ratio. *Supra* 62-65. Although limitation (c) of claim 1 discusses binding (a.k.a. associating) and dissociating, Chugai appears to assert that a POSITA would ignore the association rate constant and dissociation rate constant that define KD because a POSITA would only consider the KD ratio in the preceding limitation. *Id.* But as explained in Alexion's opening brief, the KD ratio cannot stand as a proxy for the dissociation required by the claims because it cannot dictate that all antibodies that have the recited KD ratio will dissociate in the endosome in a manner that is consistent with the purported invention. *Supra* at 51-54; Parren Sur-Reply Decl. ¶ 15.

Finally, Chugai asserts that it has not ignored naturally-occurring antibodies. *Supra* at 65. Chugai suggests that Alexion offers only theoretical conjecture about a vague class of antibodies, without identifying a single antibody that satisfies the ratio. This argument is specious, at best. Alexion's other antibody product, eculizumab, predates the earliest claimed priority date of the '377 patent and was not engineered through the substitution of histidine in the variable regions of the antibody. Parren Sur-Reply Decl. ¶ 16. Chugai's testing of this antibody acknowledges that eculizumab naturally exhibits pH-dependent binding. Chugai's infringement Contentions identify eculizumab as having a ratio of KD at pH 5.8/pH 7.4 of 19. Eculizumab shows that there is nothing theoretical about Alexion's assertions related to antibodies that were

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asserted that the *in vitro* data for eculizumab show that it also meets the limitations of claim 1—a fact that Chugai does not dispute.

not engineered with histidine substitutions. Unless Chugai advocates that the Court subsume limitation (c) into the KD ratio defined in limitation (b) of claim 1, it cannot explain how a POSITA determines whether an antibody that naturally exhibits different binding under different pH conditions "dissociates" as required by the claim.

Chugai's inability to explain whether its construction encompasses Alexion's construction, coupled with its improper attempt to write limitation (c) out of the claims, shows the errors in Chugai's arguments. As Alexion has repeatedly stated, if the term means something other than the construction proposed by Alexion, then the term is indefinite.

C. "human IgG or a humanized IgG" (claims 1, 8, and 9)

Chugai's Construction	Alexion's Construction
Plain and ordinary meaning. If construction of this phrase is necessary, it should be construed to mean "a human IgG or an IgG antibody having a humanized variable region."	"An IgG antibody having a variable region and a constant region, wherein the variable region is human or humanized and the constant region is from a human antibody"

1. Plaintiff's Opening Position

A person of ordinary skill in the art would understand the plain and ordinary meaning of "human IgG or a humanized IgG," as it is written in claim 1, without the need for additional construction. (Williams Decl. ¶ 29.) The term is found in claim 1 in the phrase "wherein the antibody is a human IgG or a humanized IgG." As explained above, "Ig" means immunoglobulin, which is another word for antibody, and "IgG" is one of the five classes of immunoglobulin, along with IgA, IgM, IgD and IgE. (*Id.*) IgG can be "human," meaning that the antibody is the type of IgG produced naturally in humans, or it can be "humanized," meaning that at least a portion of the antibody is derived from a non-human species but the antibody is otherwise composed of sequences found in a human antibody. (*Id.*) Thus, claim 1 specifies that the type of antibody to be administered is a human or humanized IgG antibody, and a person of

ordinary skill in the art would understand what that means without further clarification. (*Id.*) Further support for this conclusion is found in the prosecution history, which reveals that "IgG" was added after "human," at the request of the supervising examiner, to remove any ambiguity about the scope of this antibody claim language. (*See* Ex. I, U.S. Patent Appl. No. 13/88,512, Response to Office Action, Filed Sept. 22, 2017, at 23 ("SPE Kolker helpfully suggested that the claims be amended to say 'a human IgG or a humanized IgG,' to remove any possible ambiguity. This amendment has been made.").) The prosecution history thus further confirms that the claim term is unambiguous as written, and that the plain and ordinary meaning should govern. *See U.S. Surgical Corp. v. Ethicon, Inc*., 103 F.3d 1554, 1568 (Fed. Cir. 1997) ("Claim construction is a matter of resolution of disputed meanings and technical scope, to clarify and when necessary to explain what the patentee covered by the claims, ... It is not an obligatory exercise in redundancy.").

To the extent the plain and ordinary meaning of this term must be expressly defined, it should be construed to mean "a human IgG or an IgG antibody having a humanized variable region." That is the meaning that a person having ordinary skill in the art would give to this claim term in the context of the '377 patent. (Williams Decl. ¶ 30); *see Trs. of Columbia Univ.*, 811 F.3d at 1363. As explained above, antibodies have variable regions and constant regions. The composition of the variable regions, which are further divided into complementarity determining regions ("CDRs") and framework regions ("FRs"), determines which antigens can bind to the antibody. (Williams Decl. ¶ 30.) The composition of the constant regions, on the other hand, does not determine which antigens can bind to the antibody. (*Id.*) The composition of the variable regions of an antibody, including whether it includes human or non-human sequences, is thus critically important to whether and how the antibody is able to neutralize

antigens in the bloodstream. (*Id.*)

The parties' dispute boils down to whether "humanized IgG" requires only the variable regions to be humanized, as Chugai proposes, or whether it requires the variable regions to be humanized *and* the constant regions to be human, as Alexion proposes. A person of ordinary skill in the art would understand that a "humanized IgG" means that the variable regions are humanized, without regard to whether the constant regions are fully human or have been modified. (Williams Decl. ¶ 31.) Put simply, the composition of the variable regions is what determines whether an antibody is humanized or not. (*Id.*) And conversely, the composition of the constant regions is not relevant to the characterization of an antibody as humanized. (*Id.*)

The specification of the '377 patent supports Chugai's position. The specification explains that "'[h]umanized antibodies,' also referred to as reshaped human antibodies, are antibodies in which complementarity determining regions (CDRs) of an antibody derived from a nonhuman mammal, for example, a mouse, are transplanted into the CDRs of a human antibody." ('377 patent, col. 25:32-36.) The inventors make clear in this passage that it is the CDRs, i.e., a portion of the variable regions, that determine whether an antibody is humanized, without mentioning any feature of the constant regions. Similarly, the specification states that "[h]umanized antibodies can be produced by known methods, for example, the CDR of a mouse antibody can be determined, and a DNA encoding an antibody in which the CDR is linked to the framework region (FR) of a human antibody is obtained." ('377 patent, col. 31:55-59.) Again, this passage relies on the features of the variable regions—CDRs and FRs—to explain what makes an antibody humanized and makes no mention of the constant regions.

Alexion's special focus on the constant region is misplaced. While the specification includes statements that the constant regions may be human or are even preferably human, (*see,*

e.g., '377 patent, col. 52:36-37), such statements do not limit the scope of the claims. *See Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906-07 (Fed. Cir. 2004) (Deviating from the plain meaning of a claim term to import a limitation from the specification is improper where the patentee has not demonstrated a "clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction.'" (quoting *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002)); *ActiveVideo Networks, Inc. v. Verizon Communs., Inc.*, 694 F.3d 1312, 1326 (Fed. Cir. 2012) ("The district court did not err in concluding that these terms have plain meanings that do not require additional construction. [The] proposed construction erroneously reads limitations into the claims and the district court properly rejected that construction and resolved the dispute between the parties."). Indeed, the specification makes clear that human constant regions are not necessary and that modified constant regions can also be used:

> The constant regions used for the humanized antibodies of the present invention may be constant regions of antibodies of any isotype. ***A constant region of human IgG is preferably used, though it is not limited thereto***….The variable and constant regions of chimeric and humanized antibodies of the present invention ***may be modified by deletion, substitution, insertion, and/or addition***, and such, so long as the binding specificity of the original antibodies is exhibited.

('377 Patent, col. 32:27-39 (emphasis added).) Likewise, in the context of one antibody example, the specification states that "[t]he constant region is preferably a human antibody constant region. ***Alternatively, the constant region may be a modified form*** including substitution, deletion, addition, and/or insertion in the amino acid sequence of human IgG1, human IgG2, or human IgG4 constant regions." ('377 patent, col. 52:36-40 (emphasis added).) Alexion's construction, proposing that a humanized IgG must include a constant region "from a human antibody," is therefore not supported by the intrinsic evidence and must be rejected.

Thus, to the extent "human IgG or humanized IgG" requires construction at all, it should

be construed to mean "a human IgG or an IgG antibody having a humanized variable region."

2. Defendant's Answering Position

a. A Person of Ordinary Skill in the Art Would Understand that a Human or Humanized Antibody Includes a Human Constant Region

The parties appear to agree that a "human IgG" requires human variable regions and constant regions from a human IgG.[29] Chugai characterizes the dispute as whether a "humanized IgG" similarly requires a constant region from a human IgG, as Alexion proposes, or whether it requires considering only the variable region, because Chugai asserts that the constant region does not affect whether an antibody is considered a humanized IgG. *Supra* at 71-72. While Alexion agrees that a prerequisite for a humanized antibody is that it have a variable region that is considered humanized, e.g., includes human frameworks with CDRs from a different species, Alexion disagrees that the definition of a humanized antibody does not require an understanding of the source of the constant region. Parren Decl. ¶ 73. No person of ordinary skill in the art would describe an antibody with a humanized variable region and a murine constant region as a humanized antibody. *Id*. But if, as Chugai suggests, the term "requires only the variable region to be humanized," then any antibody with that configuration discussed in the previous sentence would satisfy this limitation. *Id*. If an antibody does not include a constant region from a human antibody, it is neither human nor humanized. *Id*.

The intrinsic evidence supports this position. In defining "humanized antibodies," the specification explains that the antibody is a reshaped human antibody "in which complementary determining regions (CDRs) of the antibody [are] derived from a nonhuman mammal." '377

[29] Alexion agrees that a person of ordinary skill in the art would understand that different subclasses of antibodies exist, e.g., IgA, IgM, IgD, IgE, and IgG, and that these claims encompass the IgG subclass only.

patent, 25:32-36. The definition does not describe the constant regions as coming from anything other than a human antibody. That would be inconsistent with the description of the antibodies as "reshaped human antibodies." *Id*., 25:32-33; Parren Decl. ¶ 74. The patent further explains that "humanized antibodies" include human IgG constant regions that can be selected from the subtypes of IgG antibodies, i.e., IgG1, IgG2, IgG3, and IgG4. '377 patent, 32:24-30. Chugai suggests that the language subsequent to this citation supports a conclusion that the constant region need not come from a human antibody. *Supra* at 73, citing '377 patent, 32:27-29. The cited language does not support this conclusion. The first sentence explains that a humanized antibody may include a constant region from any isotype, i.e., IgA, IgM, IgD, IgE, or IgG. '377 patent, 32:27-31; Parren Decl. ¶ 74. The language "[a] constant region of human IgG is preferably used, though is not limited thereto" would not teach a person of ordinary skill in the art that the constant region does not have to come from a human. *Id*. The language selects a preference for the isotype IgG over IgA, IgM, IgD, or IgE, but reiterates that the specification discloses use of these other isotypes. *Id*. It does not suggest that the constant region can be non-human. The specification teaches that the constant region of a humanized IgG is that of a human antibody and, at most, it includes point mutations in a constant region.[30] '377 patent, 76:1-24, SEQ ID NOs: 28-32 at cols. 119-129; Parren Decl. ¶ 74. In answering the question that Chugai presents – whether one must consider the constant region to determine whether an antibody is a

[30] The '377 patent teaches use of naturally-occurring human constant regions of subclasses IgG_1 and IgG_2 with the antibodies described. '377 patent, 76:1-24. The patent describes mutating an IgG_2 through substitution of amino acids at a few positions from the over three hundred amino acids positions of IgG_2. *Id*., 76:1-24, SEQ ID NOs: 28-32 at cols. 119-129. Parren Decl. ¶ 74. A person of ordinary skill in the art would understand a human IgG_2 constant region that includes point mutations may still be considered a human IgG constant region. If an antibody included that constant region and a human or humanized variable region, a person of ordinary skill in the art would describe the antibody as either a human or humanized IgG, depending on the variable region. *Id*.

"humanized IgG"—the person of ordinary skill in the art would agree with Alexion and find that such an assessment is necessary. Parren Decl. ¶¶ 4, 72, 75.

3. Plaintiff's Reply Position

A person of ordinary skill in the art knows that a humanized antibody has a humanized variable region. (Williams Reply Decl. ¶ 14.) The variable region is the region of the antibody that determines whether the antibody will bind to a particular antigen and thus have potential as a human therapeutic. Although the parties disagree about whether the constant region of the antibody is relevant to the "humanized" determination, only Chugai's construction is based on the context of the claims. In the context of the claims of the '377 patent, human or humanized IgG antibodies are injected into individual patients in order to remove an antigen from the patients' blood plasma. (*See, e.g.*, '377 patent, claim 1.) Based on this context, it would be readily apparent to a person of ordinary skill in the art that the antibodies must be suitable for human injection. (Williams Reply Decl. ¶ 13.) Alexion's argument that "an antibody with a humanized variable region and a murine constant region" is not "humanized" reveals the lack-of-context approach that plagues Alexion's claim construction positions. (*Supra* at 74.) A person of ordinary skill in the art would know that such an antibody would not be injected into a patient in the context of this invention. (Williams Reply Decl. ¶ 13.) Instead, one of skill would understand that the claimed invention requires antibodies that are suitable for human injection. (*Id.*) That is because the invention requires "identifying an individual in need of having an antigen removed from the individual's plasma" and "administering the antibody to the individual." In light of these claim requirements, it naturally follows that the antibody must be "human" or "humanized," and that is precisely why Chugai maintains that "human IgG or a humanized IgG" requires no construction; its plain meaning is apparent from the context of the

claims. To the extent construction is needed, the construction need only address the region of the antibody "that binds to the antigen through the antigen-binding domain of the antibody," which is the only region of relevance to these claims. And that region is the variable region. Thus, Chugai's construction, "a human IgG or an IgG antibody having a humanized variable region," is the construction that is faithful to the context of the claimed invention.

Alexion's construction, where the constant region must be from a human antibody, adds an unnecessarily narrow restriction on the claims and is poorly defined. Alexion has now clarified that its construction permits a constant region that is not fully human. (*Supra* at 75.) Alexion concedes that the specification encourages point mutations to be made in the constant region, rendering the constant region not fully human, and Alexion states that a person of ordinary skill in the art would still consider such a mutated constant region to be a "human" constant region. (*Supra* at 75 n.30.) This reveals the flaw in Alexion's construction. While Alexion concedes that some level of mutation in the constant region is acceptable, Alexion offers no explanation of how much mutation is permissible before the constant region ceases to be "human" and the antibody ceases to be "humanized."[31] Chugai's construction does not suffer from that flaw, because Chugai's construction reflects the understanding of a person of ordinary skill in the art, namely, that the constant region is not relevant to whether an antibody is humanized and that only the variable region matters in that determination. (Williams Decl. ¶ 31.)

[31] It is noteworthy that Alexion characterizes the accused product, Ultomiris (ravulizumab), as "humanized," even though it does not have fully human constant regions. (Ex. D at 16 ("Ravulizumab-cwvz, a complement inhibitor, is a humanized monoclonal antibody (mAb) produced in Chinese hamster ovary (CHO) cells.").) According to the label, the constant regions of ravulizumab "include the human kappa light chain constant region, and the protein engineered 'IgG2/4' heavy chain constant region." (*Id.*)

And Chugai's construction reflects the teaching of the specification, which makes clear that humanized antibodies are determined by the CDR regions of the antibody, which are part of the variable region, not the constant region. (*See, e.g.*, '377 patent, col. 25:32-36 ("'[H]umanized antibodies', also referred to as reshaped human antibodies, are antibodies in which complementarity determining regions (CDRs) of an antibody derived from a nonhuman mammal, for example, a mouse, are transplanted into the CDRs of a human antibody."); *id.* at col. 31:55-59 ("[H]umanized antibodies can be produced by known methods, for example, the CDR of a mouse antibody can be determined, and a DNA encoding an antibody in which the CDR is linked to the framework region (FR) of a human antibody is obtained.").).[32]

Alexion's proposal to limit the "humanized" claim term to require a human constant region is not supported by the intrinsic evidence or the understanding of a person having ordinary skill in the art and should be rejected.

4. Defendant's Sur-Reply Position

a. Contrary to Chugai's construction, a POSITA would look at the constant region before concluding whether an IgG is human or humanized

To show the error in Chugai's assertion that a POSITA would not review the constant region of an antibody in determining whether the antibody is humanized, Alexion explained that ignoring the constant region allows Chugai's construction to encompass, e.g., an antibody with a humanized variable region and a murine constant region. *Supra* at 74. Chugai seeks to sidestep

[32] Alexion's reliance on the "reshaped human antibody" language from the specification does not support Alexion's position that a "humanized" antibody requires a human constant region. The patent does not define "reshaped human antibody" or otherwise indicate that it means a human constant region must be present. Chugai does not dispute that humanizing an antibody can be viewed as a reshaping process, but the degree of reshaping that results in a humanized antibody depends on the modifications made to the variable region, not the constant region. (Williams Reply Decl. ¶ 14.)

this example by asserting that a POSITA would not administer that antibody with a murine constant region and humanized variable region to a patient.[33] *Supra* at 76. But Chugai does not explain how, if a POSITA would not consider the constant region to determine if an IgG is humanized, the presence of a murine constant region excludes such an antibody from its proposed construction. Parren Sur-Reply Decl. ¶ 17. Instead, Chugai looks to other terms in the claim, such as "administering," to support its preference. But that does not answer the crux of the dispute as articulated by Chugai—"[t]he parties' dispute boils down to whether 'humanized IgG' requires only the variable region be humanized, as Chugai proposes, or whether it requires the variable region to be humanized *and* the constant regions to be human." *Supra* at 72. As Alexion's responsive brief shows, a POSITA would consider the constant region. *Supra* at 74-76. If a POSITA did not consider the constant region as human, it would not consider the IgG to be "human or humanized."

VI. CHUGAI'S BACKGROUND OF THE TECHNOLOGY AND THE '623 PATENT

The technology and context underlying the '623 patent is largely the same as that underlying the '377 patent, which has already been briefed. An important additional feature in certain claims of the '623 patent is the amino acid histidine and its substitution into the variable region of the antibody recited in the claims. Histidine is an α-amino acid that plays many roles in the body, including roles in immunity, gastric secretion, and blood cell manufacture, among other roles. (Declaration of John Williams ("Williams '623 Decl." ¶ 6.) Amino acids, such as histidine, are the building blocks of antibodies, and various combinations of amino acid sequences give rise to millions of unique antibodies, including many that have been or will be engineered to facilitate the treatment of disease. (*Id.*)

[33] Therapeutic murine antibodies, e.g., Zevalin®, are administered to patients even today.

The structure of histidine includes an imidazole ring, which is part of the side chain of the histidine molecule and which renders the overall charge of histidine susceptible to relatively small changes in pH. (*Id.* ¶ 7.) The overall charge of histidine is affected by protonation, which means the degree to which a (positively charged) proton is bound to the imidazole ring. (*Id.*) Generally speaking, at lower pH, e.g., less than ~ pH 6, the imidazole ring in an isolated histidine is protonated and therefore bears a positive charge. (*Id.*) The positive charge is equally distributed between both nitrogens on the ring. (*Id.*) As the pH increases, one of the protons more readily dissociates such that at pH 7.4, the overall charge of histidine becomes more neutral. (*Id.*) As explained in the '623 patent, "histidine residues are not charged and function as hydrogen atom acceptors under neutral conditions (pH 7.4), while they become positively charged and function as hydrogen atom donors under acidic conditions (pH 5.5 to 6.0)." (Ex. F ("'623 patent") at col. 59:17-21.) This property of histidine is an important feature of the inventions claimed in the '623 patent, certain of which require one or more histidine substitutions in the variable region of the recited antibody, where antigen binding takes place. (*Id.*, claim 9.) Given its pH-dependent properties, histidine can play a significant role in the overall antigen-binding properties of antibodies at various pH values. (Williams '623 Decl. ¶ 7.) The role of histidine in the overall antigen-binding properties of an antibody is influenced by other local side chains in the antibody and the orientation of those side chains with respect to the structure of the antibody, i.e., whether they are solvent-exposed or buried within the antibody. (*Id.*)

VII. ALEXION'S BACKGROUND RELEVANT TO THE ASSERTED CLAIMS OF UNITED STATES PATENT NO. 10,472,623

A. Claim 9 of the '623 patent focuses on the substitution of at least one histidine in a variable region to achieve a result[34]

Chugai's assertion of claim 9 of U.S. Patent No. 10,472,623 ("the '623 patent") introduces a new claim construction issue for the Court, because claim 9 requires engineering a new antibody by substituting at least one histidine into the heavy and/or light chain variable regions of the antibody. Ex. F, Claim 9. Declaration of Paul W.H.I. Parren, Ph.D. in Support of Alexion's Claim Construction Answering Brief for U.S. Patent No. 10,472,623 ("Parren '623 Decl.") ¶ 5. The claim also requires the antigen-binding domain of this new antibody to bind with an antigen and, as evidenced by the KD ratio recited in the claim, requires that pH affect that binding. *Id*. Chugai argues that these three requirements are distinct and unrelated attributes of the claim 9 antibody. *Infra* at 85-88. In presenting its argument, Chugai leaves unaddressed repeated teachings throughout the specification that the addition of histidine into the variable region of the newly engineered antibody enhances the antigen-removal capability of the antibody by providing a certain KD(pH5.8)/KD(pH7.4) value,[35] i.e., the difference in affinity for the antigen under different pH conditions. *See*, e.g., '623 patent, 5:26-38, 10:65-11:3, 11:25-41, 13:10-28, 22:36-50, 29:30-38, 82:24-34, 83:24-30, 84:6-21, 85:3-30.

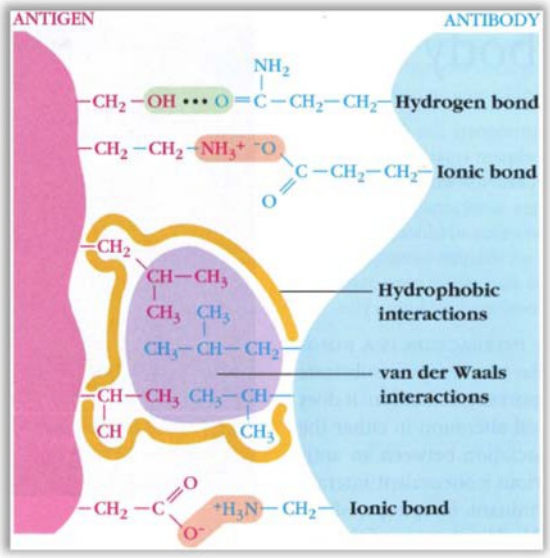
Unable to address the teachings of the specification, Chugai seeks refuge in an argument that antibody-antigen binding is more complex than simply swapping in one or more histidines to achieve a pH-dependent antigen-binding antibody. Alexion concurs that introducing a histidine into the variable region of an antibody is not a "magic bullet" that will

[34] Alexion's claim construction arguments in this section apply to claims 9, 10, 13, 14, and 20 of the '623 patent.
[35] As used herein, the term "KD ratio" refers to the KD(pH5.8)/KD(pH7.4) value of an antibody.

cause any antibody to have a weaker affinity, i.e., higher KD value, under acidic pH conditions compared to the affinity under neutral pH conditions. In most instances, that approach will not work. But the patent specification expressly connects substituting histidine into the variable region of the antibody with achieving certain results, e.g., the ability of the antibody to remove the antigen from plasma and a specified KD ratio. In light of the specification, a person of ordinary skill in the art ("POSITA") would read the claims to require that substituting one or more histidines into the variable region causes the antibody to exhibit pH-dependent binding, i.e., to have a KD(pH5.8)/KD(pH7.4) value which is in the range of 10 to 1000. Declaration of Paul W. H. I. Parren, Ph.D. in Support of Alexion's Claim Construction Answering Brief For U.S. Patent No. 10,472,623 ("Parren '623 Decl.") ¶ 4 (Claim 9).[36]

B. The effect of histidine protonation on antigen-antibody binding

Antigen-antibody binding depends on four types of noncovalent forces: (1) hydrogen bonds; (2) ionic bonds between oppositely charged side chains of amino acids; (3) hydrophobic interactions; and (4) van der Waals interactions. Exhibit 6 to Parren '623 Decl. ("Kuby"), Figure 6- 1 at 138. These noncovalent forces operate over a very short distance and are individually weak. *Id*. at 137. They require a close fit between the portions of the antibody (CDRs) and antigen (epitope)[37] responsible for the antibody-antigen binding, and the presence of several of these forces can result in a strong antigen-antibody interaction. *Id*. at 137; Parren '623 Decl.



[36] Claims 13 and 20 require a KD ratio in the range of 40 to 400.
[37] The epitope of an antigen is the collection of amino acids on the antigen that interact with the complementarity-determining regions (CDRs) of an antibody to cause the antigen and antibody to bind. Exhibit 6 to Parren '623 Decl. at 137; Parren '623 Decl. ¶ 10.

¶¶ 9, 10. The noncovalent forces vary in strength; an ionic bond is one of the strongest. Exhibit 7 of Parren '623 Decl., at 227. The combined force of the noncovalent interactions between the CDRs and the epitope affects the affinity, i.e., the equilibrium dissociation constant (KD), of the antigen-antibody binding. Kuby at 137-138. When the combined forces strengthen, there is stronger affinity between the antigen and the antibody, and the KD decreases. Parren '623 Decl. ¶ 11. A decrease in these forces results in a weaker affinity, with a corresponding increase in KD. *Id*.

As noted above, an ionic bond between an antibody and an antigen is affected by the electrical charge of the side chains of the amino acids. Parren '623 Decl. ¶ 12. Chugai's expert Dr. Williams explains that the imidazole ring that is part of the histidine molecule gains a proton to become positively charged at a pH of less than about pH 6. Williams '623 Decl. ¶ 7. The transition of the imidazole portion from a neutral state to a positive charge can affect antigen-antibody binding in various ways. Parren '623 Decl. ¶ 15. If the side chain of histidine on the antibody is in close proximity to a positively-charged side chain on the antigen, when histidine is protonated the two positive charges (on the histidine of the antibody and on the side chain of the antigen) will repel one another. Parren '623 Decl. ¶ 13. If the histidine side chain is in close proximity to a negatively-charged side chain on the antigen, when histidine is protonated at low pH, the opposite charges will attract one another.[38] *Id*. at ¶ 14. If the side chain of the histidine of the antibody is close to a charge-neutral side chain on the antigen, then an ionic bond will not form and histidine protonation will not affect binding. *Id*. at ¶ 17.

[38] The '623 patent provides examples of these two results when discussing FEBS Letters (vol. 309, No.1, 85-88, 1992), which shows weaker binding under acidic conditions upon histidine substitution, and WO 2003-105757, which shows stronger binding under acidic conditions upon histidine substitution. '623 patent at 59:26-40; Parren '623 Decl. ¶¶ 13, 16.

The location and orientation of the side chain of histidine may also cause it to have no effect on the binding between the antigen and the antibody, for several reasons. Parren '623 Decl. ¶ 17. First, the histidine side chain may not be sufficiently close to the antigen to affect binding, or it may be surrounded by negatively-charged side chains on the antibody that counteract the positive charge. *Id*. Further, the histidine may be "buried" by other amino acids of the antibody so that the histidine is unavailable for binding or not exposed to a changing pH environment. *Id*. These facts support the view that antigen-antibody binding is complex, unpredictable, and specific to the particular antibody and antigen involved (including the specific amino acid sequences and three-dimensional structures of the particular antibody and antigen). *Id*. at ¶ 18. However, they do not negate the claim language and the express teachings of the specification that lead a POSITA to understand that the histidine substitution recited in claim 9 must be what provides the antibody with the claimed KD ratio. *Id*.

VIII. CHUGAI'S DISPUTED CONSTRUCTIONS FOR THE '623 PATENT

A. Disputed Constructions for the '377 Patent

The parties have fully briefed the disputed constructions for the following claim terms from the '377 patent:

- "KD for the antigen"
- "dissociates from the bound antigen under conditions present in an endosome in vivo"
- "human IgG or a humanized IgG"

These claim terms also appear in the '623 patent, and the parties have agreed that the constructions should be the same for both the '377 patent and the '623 patent. Accordingly, no additional briefing specific to the '623 patent is necessary regarding these terms.

B. "the antibody binds to the antigen through the antigen-binding domain of the antibody comprising one or more histidine substitutions at one or more heavy chain or light chain variable region positions and has a KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000"

Chugai's Construction	Alexion's Construction
Plain and ordinary meaning. The plain and ordinary meaning of this phrase requires the antibody to have three characteristics. First, the antibody must bind to the antigen through the antigen-binding domain of the antibody. Second, the antibody must have one or more histidine substitutions in the heavy chain variable region or light chain variable region. Third, the antibody must have a KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000.	"The antibody binds to the antigen through the antigen-binding domain of the antibody comprising one or more histidine substitutions at one or more heavy chain or light chain variable region positions in a preexisting antigen-binding domain, whereby the histidine substitution provides the antibody with a KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000"

1. Chugai's Construction is Faithful to the Intrinsic Evidence

A person of ordinary skill in the art would understand the plain and ordinary meaning of this claim term without the need for additional construction. (Williams '623 Decl. ¶ 9.) The term is found in independent claim 9, which is directed to a method of removing an antigen from a patient's plasma, whereby an antibody with certain characteristics is administered to the patient, binds to the antigen, and then dissociates from the bound antigen in the endosome, which frees up the antibody to be recycled back into plasma to bind with other antigens. ('623 patent, claim 9.) The disputed claim term sets forth three characteristics that the antibody must have in order to fall within the scope of the claimed invention. Each of these characteristics would be readily understood by a person of ordinary skill in the art and none require any special construction. (Williams '623 Decl. ¶ 10.)

First, the antibody must bind to the antigen through the antigen-binding domain of the antibody. This claim element requires no further construction, because its meaning would be clear to a person of ordinary skill in the art. (Williams '623 Decl. ¶ 11.) *See Phillips v. AWH*

Corp., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (claim terms "are generally given their ordinary and customary meaning" (citation omitted)). As explained in the specification, the antigen-binding domain of an antibody includes the complementarity determining region ("CDR") and is not limited to specific amino acid sequences:

> The antigen-binding domain of an antibody includes, for example, CDR and variable region. When the antigen-binding domain of an antibody is CDR, the antigen-binding molecule may include all of the six CDRs of a whole antibody, or one, or two or more of them. Alternatively, when an antigen-binding molecule includes CDR as a binding domain of an antibody, the CDR may include amino acid deletion, substitution, addition, and/or insertion, or may be a partial CDR.

('623 patent, col. 23:42-50.) The specification further explains that "[t]he antigen-binding molecules of the present invention are not particularly limited as long as they have the specific binding activity to an antigen of interest. Preferred antigen-binding molecules of the present invention include, for example, substances having an antigen-binding domain of an antibody." ('623 patent, col. 23:37-42.) This explanation is consistent with how a person of ordinary skill in the art would understand the claimed invention, that is, the antibody must bind to the antigen and must do so through the antigen-binding domain of the antibody. (Williams '623 Decl. ¶ 11.) Indeed, Alexion does not dispute that the meaning of "[t]he antibody binds to the antigen through the antigen-binding domain of the antibody" is plain on its face, as Alexion's proposed construction merely repeats this claim language verbatim. (Joint Claim Construction Chart, D.I. 63, at 3.) Thus, no construction of this claim element is needed.

Second, the antibody must have one or more histidine substitutions in the heavy chain variable region or light chain variable region. The claim language requiring "one or more histidine substitutions at one or more heavy chain or light chain variable region positions" would be readily understood in this manner by a person of ordinary skill in the art and needs no further construction. (Williams '623 Decl. ¶ 12.) A person of ordinary skill in the art would understand

that histidine is an amino acid that is one of the building blocks of antibodies, and that histidine can be inserted into an antibody at various positions, including in the heavy chain or light chain variable region, and can replace other amino acids in an antibody depending on the application. (*Id.*) The specification is consistent with this understanding, stating that "the present invention provides methods for increasing the number of antigens that can be bound by an antigen-binding molecule by substituting histidine for at least one amino acid in the antigen-binding molecules or inserting at least one histidine into the antigen-binding molecules." ('623 patent, col. 10:11-16.) The specification provides further details on the flexibility of histidine substitution:

> A histidine or non-natural amino acid may be substituted or inserted at any site. Preferred sites of histidine or non-natural amino acid substitution or insertion include, for example, sites within a region that has an impact on the antigen-binding ability of the antigen-binding molecule. For example, when the antigen-binding molecule is an antibody, such sites include an antibody variable region or CDR. The number of histidine or non-natural amino acid mutations is not particularly limited. Histidine or non-natural amino acid may be substituted or inserted at a single site, or at two or more sites. Furthermore, a deletion, addition, insertion, and/or substitution of other amino acids may be introduced simultaneously with the histidine or non-natural amino acid substitution or insertion.

('623 patent, col. 22:43-57; *see also id.* at col. 13:9-42, col. 22:58 - 23:20, col. 29:24-45, col. 30:56 - col. 31:25, col. 48:34 - col. 50:45.) Thus, a person of ordinary skill in the art would understand that the claimed antibody must have one or more histidine substitutions in the heavy chain variable region or light chain variable region and would understand what that means without further explanation. (Williams '623 Decl. ¶ 12.)

Third, the antibody must have a KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000. Once again, this claim element would be understood by a person of ordinary skill in the art as written and requires no special construction. (Williams '623 Decl. ¶ 13.) A person of ordinary skill in the art reading

the claims and specification would understand that the inventors characterized an important feature of their invention in terms of the dissociation constant (KD), which is a measurement of the propensity of an antibody to separate from its target antigen, and which can change for a given antibody-antigen pair depending on the pH of the surrounding environment. (*Id*.) The inventors discovered that the ratio of KD values at different pH values, e.g., the KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD at pH 5.8 and at pH 7.4, is an important indicator of whether antibody recycling would occur, and the claims of the '623 patent include various KD ratios. (*See, e.g.*, '623 patent, claim 9, 11-13.) The specification explains the KD ratio for the claimed inventions as follows: "the value of KD(pH5.8)/KD(pH7.4), which is a ratio of dissociation constant (KD) against an antigen at pH 5.8 and that at pH 7.4, is preferably 2 or greater, more preferably 10 or greater, and still more preferably 40 or greater." ('623 patent, col. 12:30-34.) And the specification extensively describes KD testing and lists KD(pH5.8)/KD(pH7.4) data for various antibodies. (*See, e.g.*, '623 patent, col. 65:60 - 66:48, col. 85:33 - 86:34.) In light of these disclosures, a person of ordinary skill in the art would understand the concept of the KD ratio as recited in the claims, i.e., "a KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000" without further explanation, and the plain and ordinary meaning of that language should govern. (Williams '623 Decl. ¶ 13.)

In sum, the disputed claim term of the '623 patent should be given its plain and ordinary meaning, which requires that the recited antibody have three characteristics, namely, the antibody must (1) bind to the antigen through the antigen-binding domain of the antibody; (2) have one or more histidine substitutions in the heavy chain variable region or light chain variable region; and (3) have a KD(pH5.8)/KD(pH7.4) value within the specified numerical range.

2. Alexion's Construction Adds Improper Limitations and Should Be Rejected

Alexion's construction of the disputed term adds improper limitations and is not faithful to the intrinsic evidence, as understood by a person having ordinary skill in the art. Alexion seeks to introduce a narrowing limitation, "in a preexisting antigen-binding domain," that is unnecessary and a second limitation, "whereby the histidine substitution provides the antibody with [the recited KD ratio]," that is legally and scientifically flawed.

Alexion's proposal to append the histidine substitution claim language with "in a preexisting antigen-binding domain" does nothing to elucidate the plain meaning of the disputed claim term. *See InterDigital Communs., LLC v. ITC*, 690 F.3d 1318, 1324 (Fed. Cir. 2012) ("The plain meaning of claim language ordinarily controls.") (citing *Phillips*, 415 F.3d at 1316). Chugai agrees that "substitution" generally connotes that something was inserted in place of something else. But Chugai disagrees that the concept of a "preexisting antigen-binding domain" needs to be part of the construction here. The claim language "histidine substitutions" is plain on its face, and Alexion has not identified any ambiguity in that term that requires a construction. Alexion's proposal merely adds more words to unambiguous language, an approach that is disfavored in claim construction. *See U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) ("Claim construction is a matter of resolution of disputed meanings and technical scope, to clarify and when necessary to explain what the patentee covered by the claims, ... It is not an obligatory exercise in redundancy.")

Alexion's other proposal, to include "whereby the histidine substitution provides the antibody with [the recited KD ratio]," should also be rejected. With this additional language, which is not found in the specification, Alexion attempts to import a causation element into the claims. That is, Alexion seeks to construe the claim term to require that the histidine

substitution, by itself, performs a function that causes the recited KD ratio. Alexion's proposal is flawed for several reasons.

First, Alexion is wrong as a scientific matter. Chugai does not dispute that the inclusion of histidine in the recited antibody *contributes* to the KD ratio for the antibody. But to the extent Alexion argues that the histidine substitution is the *sole cause* of the KD ratio, Alexion's position is unfounded. The KD ratio of an antibody at two different pH values is the result of the overall composition of the antibody, not a single amino acid. (Williams '623 Decl. ¶ 14.) Nothing in the specification is to the contrary. While the histidine substitutions recited in the claims play an important role in the association and dissociation of the recited antibodies from their target antigens, and hence contribute to the KD values, histidine alone does not dictate the KD values. (*Id.*) As explained above, the role of histidine in the overall antigen-binding properties of an antibody is influenced by other local side chains in the antibody and the orientation of those side chains with respect to the structure of the antibody, i.e., whether they are solvent-exposed or buried within the antibody. (*Id.*) Alexion's attempt to attribute the recited KD ratio solely to histidine substitution is therefore wrong from a scientific standpoint.

Second, Alexion's effort to import a functional limitation into the claims is legally improper. The asserted claims are method claims that use "comprising" language, meaning they are open-ended claims that are not limited to the recited elements. *See Invitrogen Corp. v. Biocrest Manufacturing, L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."). Consequently, proposing that there is a closed causal relationship between the recited histidine and KD ratio, where unclaimed elements are excluded from contributing to the KD ratio, is inconsistent with the open-ended scope of the "comprising" claim device. *See*

Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501 (Fed. Cir. 1997) ("'Comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."). This is particularly problematic here, where it is known that histidine alone does not cause the KD value of a given antibody. (Williams '623 Decl. ¶ 14.)

Finally, apart from its scientific and legal flaws, Alexion's attempt to import a functional limitation into the claims is simply unnecessary. As explained above, the meaning of the disputed claim term is plain on its face and requires the recited antibody to have three characteristics. None of those characteristics are ambiguous or require any special construction, least of all a construction with a functional or causal element. *See Transmatic, Inc. v. Gulton Indus., Inc*., 53 F.3d 1270, 1278 (Fed. Cir. 1995) ("The district court erred by importing unnecessary functional limitations into the claim.").

For these reasons, Alexion's proposed construction should be rejected.

IX. ALEXION'S DISPUTED CLAIM TERM

A. "The antigen binding domain . . . comprising one or more histidine substitutions . . . and a KD(pH5.8)/KD(pH7.4) value . . . of 10 to 1000"

The parties' dispute concerning this claim language can be summed up in two questions: (1) what are the one or more histidine substitutions being substituted for; and (2) what is the effect of those substitutions? On the first question, Alexion proposes that in order for an amino acid substitution to occur, a known sequence for an antigen-binding domain must exist before an amino acid in that antigen-binding domain can be substituted with a histidine, as required by the claims. Chugai appears to generally agree with Alexion on this point but will not acknowledge the fact that a substitution always requires a preexisting amino acid sequence. *Supra* at 89.

On the second question, Alexion proposes that the histidine substitution must be what provides the antibody with the claimed KD ratio. Chugai proposes that the claimed substitution can have no effect on the antibody's characteristics. Under Chugai's construction, the histidine substitution does not necessarily relate to the KD ratio required by the claim. *See Supra* at 88 (discussing the claim elements as "three characteristics" of the antibody). In other words, Chugai's construction does not require a nexus between the histidine substitution and achieving the KD ratio. A review of the intrinsic record shows that a nexus must exist.

1. The plain meaning of "substitution" requires that a precursor exist

Alexion proposes that a POSITA would understand the term "the antigen-binding domain of the antibody comprising one or more histidine substitutions at one or more heavy chain or light chain variable region positions" requires that an antigen-binding domain existed prior to a substitution, and that at least one of the amino acids within that existing antigen-binding domain is substituted with a histidine. Parren ’623 Decl. ¶ 3. This is consistent with the plain meaning of the term "substitution," which requires the act of using something instead of another thing.[396] In order to use something instead of another thing, the other thing must exist. Chugai appears to largely accept this position because it states that it "agrees that 'substitution' generally connotes that something was inserted in place of something else." *Supra* at 89. But Chugai's qualified acceptance ("generally connotes") demonstrates the need for the Court to construe the claim term and to adopt Alexion's proposal that the claim requires a preexisting antigen-binding domain. Chugai’s selection of the phrase "substitution **generally** connotes" encompasses situations where

[39] *See*, Oxford Cambridge Dictionary definition available at https://dictionary.cambridge.org/us/dictionary/english/substitution.

"substitution" does not connote insertion of one thing in place of another thing. *Id.* (emphasis added). However, Chugai provides no explanation as to when the term either connotes or does not connote that one thing is inserted in place of another thing.

The specification describes several ways to obtain a preexisting antigen-binding domain sequence to later mutate with a histidine substitution. Parren '623 Decl. ¶ 25. A POSITA can select a known sequence, or a POSITA can generate a new antigen-binding domain sequence. '623 Patent, 33:7-16. The POSITA can then mutate the known sequence or the new antigen-binding domain sequence. *Id.*; *see also* 40:58-41 (explaining use of preexisting antibodies, preexisting libraries, new antibodies, or new libraries by which mutated antibodies are generated by substituting histidine into the above-described antibodies and libraries); Parren '623 Decl. ¶¶ 8, 25. In each instance, the patent describes that something existed before the substitution with histidine occurred. *Id.* Further support exists in the patent where the specification describes generating the few antibodies that exhibit pH-dependent binding. *See* '623 patent 49:2-48, Tables 1 and 5 (describing heavy chain variable regions (e.g., H3pI, H170, and CLH5) generated by ,mutating the existing variable heavy chain H52 and light chain variable regions (e.g., L73, and L82)), 82:24-50 (generating engineered anti-IL-6 antibodies by mutating wild type (WT) amino acid sequences SEQ ID NO: 62 and SEQ ID NO: 63), 84:5-27 (generating engineered anti-IL-31 receptor antibody by mutating wild type (WT) amino acid sequences SEQ ID NO: 67 and SEQ ID NO: 68). Parren '623 Decl. ¶ 22.

Based upon the plain meaning of the claim language and the teachings of the specification, the Court should include within its construction that the "histidine substitution" occurs in a variable region of an existing antigen-binding domain. Leaving out this requirement would result in a construction that does not give meaning to the word "substitution."

2. The histidine substitution provides the claimed KD ratio

Claim 9 requires a method of removing an antigen from plasma by administering an antibody with certain pharmacological characteristics that allow the antibody to clear the antigen. The patent explains that the antibody is engineered through the substitution of histidine to maintain binding under plasma pH conditions (pH 7.4) but causes reduced binding under endosomal pH conditions (pH 5.8). ’623 patent, 59:41-53. This pH-dependent binding is reflected by the KD ratio recited in the claim. ’623 patent, 11:62-12:4, 82:67-83:20, 84:47-66, 86:19-23. The '623 patent specification and Chugai's arguments during prosecution to secure issuance of claim 9 make it clear that the fundamental feature of the alleged invention is that the histidine substitution "provides"—or conveys, or is the cause of—the pharmacological property of the claimed KD ratio. The histidine substitution in the engineered antibody is therefore inextricably tied to the KD ratio, and the claim should be construed accordingly.

The "Problems to be Solved by the Invention," the "Means of Solving the Problems," and the "Mode For Carrying out the Invention" emphasize the crucial role of the histidine substitution to the KD ratio. ’623 patent, 3:35-48, 4:11-16, 5:26-38, 10:59-11:3. The "objective" of the alleged invention is to "provide methods for binding antigen-binding molecules to the antigens multiple times and methods for improving the pharmacokinetics of antigen-binding molecules," which is achieved by "impairing the antigen-binding activity of the antigen-binding molecule at pH 5.8 as compared to that at pH 7.4." *Id.*, 3:39-43, 4:28-36. And the only mode for improving the pharmacokinetics—the purported ability of an antibody to bind multiple antigens to remove those antigens—is precisely what is required by claim 9: substituting histidine in the antigen-binding molecule. E.g., *Id.*, 9:61-66, ("[T]he present invention provides methods for increasing the

number of times of antigen-binding in antigen- binding molecules by substituting histidine for at least one amino acid in the antigen-binding molecules…"); *see also* '623 Patent, 5:26-37 ("[A] method for increasing the ability . . . to eliminate antigen in plasma by substituting at least one amino acid of the antigen-binding molecule with histidine . . . wherein the histidine substitution . . . increases the KD(pH5.8)/KD(pH7.4) value . . . "); *see also Id.*, 10:59-11:3, 11:15-18, 11:25-41, 13:10-27. Chugai's decision to draft claim 9 to include limitations to both a histidine substitution and the desired KD ratio compels the conclusion that the histidine substitution is directly linked to the KD ratio. Indeed, claim 9 expressly limits the location of the histidine substitution to the variable region, the region of the antibody directly responsible for mediating antigen binding.

Elsewhere, the specification demonstrates the direct link between histidine substitution and the ability of a histidine-substituted antibody to remove antigen because the antibody exhibits the claimed KD ratio.[40] The patent describes that an antibody's pH-dependent binding, as reflected by the KD ratio described in the claims, may be achieved in protein-protein interactions "by substituting an amino acid residue involved in the protein-protein interactions with a histidine residue, or by introducing a histidine into an interaction site."[41] '623 patent, 59:25-29. The patent teaches that the location of the histidine substitution is not limited provided that the substitution has its intended effect. "**Such histidine mutation (substitution)** or insertion sites are not particularly limited and any **is acceptable as long as** the antigen-binding activity at pH

[40] Although the patent links the KD ratio to the ability of an antibody to remove antigen from plasma, Alexion disputes whether the KD ratio is in fact indicative of this ability. *See Supra* at 50-53.

[41] As shown by citations within the '623 patent, the patentees neither identified this property of histidine nor were the first to exemplify the use of histidine substitution to generate antibodies with pH-dependent binding properties. '623 patent, e.g., at 13:14-21, 59:25-40, 60:19-22.

5.8 is lowered than that at pH 7.4 (**the value of KD(pH5.8)/KD(pH7.4) gets greater**) as compared to before mutation or insertion." *Id*. at 13:21-26 (emphasis added); 29:30-38. These general teachings of the specification link the histidine substitution to achieving the pH-dependent binding property of an antibody. Parren '623 Decl. ¶ 7. The examples of the patent support this link too.

Each antibody in the patent for which the patent provides a KD ratio establishes that the antibody achieved the lower limit of the ratio of the claim through at least a histidine substitution. The patent describes generating three related anti-IL-6R antibodies, H3pI/L73, H170/L82, and CLH5/L73, by substituting histidines for amino acids in the variable regions of a pre-existing antibody and provides the KD(pH5.8)/KD(pH7.4) data for these antibodies. '623 patent, 48:33-50:45, 65:60-66:48. The patent reports that the wild-type antibody has a KD ratio of 2.4, outside the range of 10 to 1000, but the antibodies that include histidine substitutions have KD ratios of 41.3, 393.5, and 66.1. *Id*., Table 5, *see also* Table 17. These data suggest that the histidine substitutions are involved in each antibody attaining the KD ratio of claims.[42] The patent's explanations concerning generating the two related anti-IL-6 antibodies and one anti-IL-31R antibody provide further evidence on this point. For both anti-IL-6 antibodies and the anti-IL-31R antibody, the patent states "to confer the pH-dependent binding ability of the antibody to bind [the antigen], histidine substitutions were introduced into the amino acids in the CDR." '623 patent, 82:24-50, 84:6-26. The KD ratio data show that, while the wild type antibodies do not exhibit the KD ratio required by claim 9, the histidine-substituted antibodies

[42] The anti-IL-6R antibodies differ from the anti-IL-6R wild type by several non-histidine substitutions in the constant and variable regions of the antibodies. The patent does not discuss the effects of these substitutions. It only attributes the development of a pH-dependent binding antibody to the substitution or insertion of at least one histidine into the variable regions of the antibodies. '623 patent, 83:25-31.

have the KD ratio required by claim 9.[43] '623 patent, Table 14 (anti-IL-6), Table 16 (anti-IL-31R).

Chugai further emphasized the causal relationship between histidine substitution and the KD ratio during prosecution of the '623 patent. The PTO rejected then-pending claim 66 (which issued as claim 9 with nearly identical language) for lack of written description. To demonstrate that the inventors had "possession" of the claim, Chugai argued that "the recited pharmacological property" in claim 66 of "a KD(pH5.8)/KD(pH7.4) value of 10 to 1000" is "**conveyed in part by the presence of the additional histidine residue or residues**," thus allowing "the antibody… to bind antigen in in [sic] a pH dependent manner, thereby resulting in a more effective removal of antigen from plasma." Exhibit 8 to Parren '623 Decl. (March 20, 2019 Amendment and Reply, at 18 (emphasis added)); Parren '623 Decl. ¶ 24.

The manifestly clear linkage that Chugai described and relied on between the histidine substitution and the KD ratio is the same kind of fundamental objective or feature of a claimed invention that the Federal Circuit has held must inform and limit the interpretation of a claim. In *Praxair v. ATMI, Inc.*, the court construed the term "flow restrictor" to add a functional limitation: "a structure that serves to restrict the rate of flow **sufficiently to prevent a hazardous situation**." *Praxair*, 543 F.3d 1306, 1324 (Fed. Cir. 2008) (emphasis added). In doing so, the Federal Circuit relied on the "fundamental feature" or "fundamental object" of the invention disclosed in the specification (i.e., flow restriction intended to prevent a hazardous release of gas) to aid in claim interpretation because the

[43] Tables 14 and 16 report data for KD(**pH5.5**)/KD(pH7.4) as opposed to KD(**pH5.8**)/KD(pH7.4). The more acidic pH used to exemplify the pH-dependent binding of these antibodies may result in a higher KD ratio. Parren '623 Decl. ¶ 23. Therefore, it is unknown whether anti-IL-6 clone 1 and clone 2 meet the KD ratio recited in claim 9.

patent made clear that the "flow restrictor" was narrower than the plain and ordinary meaning given to it by the district court. *See id.*[44] Citing *Praxair*, the court in *AVM Technologies, LLC v. Intel Corp.* 15-33-RGA, 2016 WL 4182740 *6-*9 (D. Del. Aug. 5, 2016) likewise narrowly construed a series of claim terms at issue to align their scope with the "fundamental feature" described in the specification.

In looking to the specification to understand the meaning of the claims, the courts in *Praxair*, *Microsoft*, *Alloc* and *AVM* heeded longstanding Federal Circuit precedent that claims may **not** be interpreted in a vacuum—as Chugai incorrectly urges this court to do. Claims must be viewed in light of the entire intrinsic record. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc) (the specification "is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term."); *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998) ("The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction."). The specification's repeated description of the result of histidine substitution, coupled with the data in the handful of examples of antibodies provided, would lead a POSITA to Alexion's construction. Parren ’623 Decl. ¶ 4. It is the histidine substitution that causes the antibody to achieve the KD ratio of claim 9. That is the only legitimate reading of the claims when viewed in light of the specification.

[44] *See also Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1347-48 (Fed. Cir. 2004) (claim to transmission of data between local and remote sites construed to require transmission only over telephone lines, where the patent "repeatedly and consistently" described the invention in this manner); *Alloc, Inc. v. Intern'l Trade Com'n*, 342 F. 3d 1361, 1370 (Fed. Cir. 2003) ("[W]here the specification makes clear at various points that the claimed invention is narrower than the claim language might imply, it is entirely permissible and proper to limit the claims.")

3. Chugai misrepresents Alexion's position as asserting that histidine alone causes the KD ratio

To support its broad construction untethered from the written description and the intrinsic record, Chugai incorrectly asserts that Alexion proposes that the histidine substitution is the sole cause of the KD ratio. *Supra* at 90. This is incorrect. Alexion agrees that antigen- antibody binding is complex and that a plethora of factors may affect binding affinity, i.e., the KD value of an antibody for an antigen. Parren '623 Decl. ¶ 18. For example, the amino acids within the binding regions along with the configurations of the antibody and antigen will impact the affinity of the antibody for the antigen. Parren '623 Decl. ¶¶ 11-17. The affinity of an existing or newly-expressed antibody for an antigen may differ under different conditions for numerous reasons.[45] *Id*. But these facts do not alleviate the Court's obligation to review the claims and the specification to understand the proper meaning of the claims: that the histidine substitution must be responsible for a change in the KD value, as compared to the unmodified pre-existing antibody, under acidic pH conditions such that the engineered antibody attains the KD ratio recited in claim 9.

A consideration of the common knowledge of protein-protein interactions and the disclosure of the specification shows Chugai's proposed construction is incorrect when considered from both a scientific and claim construction perspective. Chugai proposes that the three components of the claims are unrelated. *Supra* at 85-88. Under Chugai's proposed construction, all a POSITA must do to understand whether an antibody meets the limitation is to ask three questions:

(1) Does the antibody-binding domain of the antibody bind the antigen?

[45] For example, Chugai acknowledges that an earlier Alexion antibody, eculizumab, binds in a pH-dependent manner but does not include histidine substitutions in the variable region. Chugai's Infringement contentions citing WO2017/104779, Table 10.

(2) Do the variable regions include at least one histidine substitution?

(3) Does the antibody have a KD(pH5.8)/KD(pH7.4) value within 10 to 1000?[46]

If the answer to all these questions is yes, then the antibody meets the limitation. Chugai's construction is wrong because it divorces the structural substitution of question (2) from the functional outcome of question (3). Parren '623 Decl. ¶¶ 20, 21.

The following hypothetical elucidates Chugai's unsupportable position. Assume we start with an antibody that naturally exhibits a weaker affinity at pH 5.8 compared to its affinity at pH 7.4. The difference in binding affinity at pH 5.8 and pH 7.4 causes the antibody to have a KD ratio of 20 when dividing its KD(pH5.8) by its KD(pH7.4).[47] A new antibody is generated that includes a histidine substitution in one variable region and the new antibody maintains a KD ratio of 20, and thus the antibodies have the exact same pH-dependency.[48] Despite the fact that the histidine has no effect on the pH-dependent binding of the antibody, the new antibody falls within Chugai's construction because it binds an antigen, has a histidine substitution, and exhibits the claimed KD ratio. Even more damaging to Chugai's position, assume that the histidine substitution causes the new antibody to exhibit a higher affinity at pH 5.8 to its

[46] Chugai asserts that the KD ratio is a key component of the inventor's discovery because it "is an important indicator of whether antibody recycling would occur." *Supra* at 88. It is unclear what Chugai means by "indicator of whether antibody recycling will occur," because FcRn mediated recycling of antibodies occurs whether the antibody is bound or unbound to an antigen. '623 patent at Figure 4 (showing FcRn recycling both bound (left panel) and unbound (right panel) antibody. If Chugai means that the KD ratio is an indicator of whether the antibody will recycle in a bound or unbound form, as explained in Dr. Parren's first declaration at ¶¶ 60- 63, the KD ratio is an unreliable indicator of this fact, because two antibodies with the same KD ratio can behave drastically differently *in vivo*.

[47] This is not too difficult to imagine considering that Chugai has published data that show the antibody eculizumab has a KD ratio of 19. *See Supra* at 99, Fn. 45.

[48] As explained in section I.B above, there are several reasons a histidine substitution in a variable region of an antibody may not affect antigen-antibody binding. Parren '623 Decl. ¶ 17.

antigen, i.e., causes the KD ratio to become lower.[49] As long as the new KD ratio does not fall below 10, the new antibody would meet claim 9 under Chugai's construction, even though the result of the histidine substitution is the exact opposite of what the patent teaches. '623 patent at 13:21-26, 29:30-38, 59:26-40, 82:24-29, 84:6-11. The Court should reject Chugai's construction as counter to the teachings of the patent. *AVM Technologies, LLC*, 2016 WL 4182740, at *9 (Chugai's construction " constitute(s) a wholesale departure from the principles set forth in the specification.")

4. Chugai's legal citations concerning the claim term "comprising" are red herrings

Chugai attempts to add legal heft to its argument by citing cases that advance the proposition that the transitional claim term "comprising" connotes an open-ended claim. *See Supra* at 90-91, citing *Invitrogen Corp. v. Biocrest Manufacturing, L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 465, 501 (Fed. Cir. 1997). But the recitation of this patent proposition is of no moment to the issues at hand. It is a red herring that tries to divert the Court from the teachings of the patent.

In *Invitrogen Corp.*, the Federal Circuit addressed a method claim that included two steps. *Invitrogen Corp.*, 327 F.3d at 1368. The district court found non-infringement because the alleged infringer included a precursor step before practicing the two steps of the method. The Federal Circuit concluded that the "comprising" language of the claim allowed for the

[49] As explained in section VII B above, if the histidine side chain is near a negatively charged portion of the antigen, the protonation may add an attractive force at pH 5.8 that does not exist at pH 7.4. Parren '623 Decl. ¶ 14. The substitution would reduce the KD of the new antibody at pH 5.8 as compared to the antibody without the histidine substitution. *Id*. Although this new force may decrease the KD at pH 5.8, it may not be sufficient to cause the KD value at pH 5.8 to match that at pH 7.4, so the engineered antibody would still have a lower KD at pH 7.4 but the difference would be less than for the unsubstituted antibody.

method to include other steps. *Id*. at 1368-1369. Similarly, the *Genentech* case applied an open- ended meaning to "comprising" in the context of the broadest reasonable interpretation standard used in reviewing patent office interference proceedings. *Genentech, Inc.*, 112 F.3d at 500-501. The claims at issue in that case required a DNA construct that included sequences to code for two proteins. *Id*. at 497. The accused product included the sequences for the proteins recited in the claim but also included additional sequence information. *Id.* at 498. The Federal Circuit concluded that the claims did not exclude the presence of other sequence information provided that the sequences for the recited proteins were present and read in such a way that the DNA construct expresses these proteins. *Id*. at 501. Both cases stand for the unremarkable proposition that a method or product can infringe a claim with the transitional phrase "comprising" if it meets all claim limitations irrespective of whether other steps or features are present.

Alexion's proposed construction does not violate this legal principle. First, as discussed in the preceding section, Alexion does not assert, as Chugai suggests, that "the histidine alone" causes the KD ratio for the antibody. *Supra* at 91 ("it is known that the histidine alone does not cause the KD value for a given antibody."). Alexion agrees that a plethora of factors can affect the affinity, i.e., KD value, of an antibody for an antigen. But the specification makes clear that the histidine substitution in an antibody of the claim must cause the antibody to bind in a pH-dependent manner in accordance with the KD ratio recited by the claims. ’623 Patent, 13:21-26, 29:30-38, 59:26-40, 82:24-29, 84:6-11. This does not foreclose other components from contributing to the KD value under neutral and acidic pH conditions. But, based upon the specification's description, the change in the difference in the KD value between neutral and acidic pH results from the histidine substitution. *Id*., 13:21-26, 29:30-38, 59:26-40, 82:24-29,

84:6-11. Unlike the cases Chugai cites to support its argument concerning "comprising," Alexion's construction does not seek to foreclose the presence of another step or the inclusion of additional structure. See *Invitrogen Corp.*, 327 F.3d at 1368; *Genentech, Inc.*, 112 F.3d at 501. Thus, those cases should not affect the Court's decision.

In view of Alexion's evidence and arguments discussed above, the Court should construe this limitation to require that the substitution into the variable region of a preexisting antigen- binding domain causes the antibody to the achieve a KD(pH5.8)/KD(pH7.4) value of 10 to 1000 (claim 9) and 40 to 400 (claims 13 and 20).[50] Simply stated, the histidine substitution provides the antibody with the claimed KD ratio.

X. CHUGAI PHARMACEUTICAL CO., LTD.'S REPLY FOR UNITED STATES PATENT NO. 10,472,623

A. Chugai's proposed construction reflects the plain and ordinary meaning of the disputed claim term

The disputed claim term has a straightforward, plain meaning that requires no special construction. The parties agree that the term requires the recited antibody to have three characteristics in order to fall within the scope of the claimed invention: 1) the antibody must bind to the antigen through the antigen-binding domain of the antibody; 2) the antibody must have one or more histidine substitutions in the heavy chain variable region or light chain variable region; and 3) the antibody must have a KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000. As Chugai's expert, Dr. Williams, has explained, each of these characteristics would be readily understood by a person of ordinary skill in the art and none require any special construction. (Williams '623

[50] Several asserted claims depend from claim 9. '623 patent, claims 9, 10, 13, 14, and 20. These arguments apply to those claims and the KD ratio recited in those claims. '623 patent, claims 13 and 20.

Decl. ¶ 10.) Each characteristic is well-supported in the specification, (*see* Chugai Op. Br. at 3-6), and there are no words that are ambiguous or require construction to elucidate their meaning.

Alexion criticizes Chugai's plain meaning construction because it "does not require a nexus between the histidine substitution and achieving the KD ratio." (Alexion '623 Argument at 92.) Alexion's cites no legal authority requiring a "nexus" between two claim elements that are plain on their face. Alexion does not allege that claim 9 is a means-plus-function claim, identifies no functional claim language that dictates the role of the "histidine substitutions," and fails to identify anything at all in the claim that would be unclear to a person of ordinary skill in the art. Instead, driven by a perceived non-infringement position, Alexion seeks to distort the meaning of the claim by injecting new limitations, including a functional limitation, that contradict the intrinsic evidence and the law. Alexion's position should be rejected, and Chugai's plain meaning construction should be adopted.

B. Alexion's proposed construction changes the plain meaning and is contradicted by the intrinsic evidence

Rather than identify words that Alexion believes a person of skill would not understand and that require clarifying construction, *see Mass. Inst. of Tech. v. Shire Pharms., Inc*., 839 F.3d 1111, 1118 (Fed. Cir. 2016) ("The purpose of claim construction is to give claim terms the meaning understood by a person of ordinary skill in the art at the time of invention.") (citing *Phillips v. AWH Corp*., 415 F.3d 1303, 1312-14 (Fed. Cir. 2005) (en banc), Alexion instead proposes to inject *additional limitations* in the claim language that completely change the meaning of the claims and that are contradicted by the intrinsic evidence, by scientific principles, and by claim construction law. Alexion's construction adds the following underlined limitations that are neither necessary nor warranted:

> The antibody binds to the antigen through the antigen-binding domain of the antibody comprising one or more histidine substitutions at one or more heavy chain or light chain variable region positions in a preexisting antigen-binding domain, whereby the histidine substitution provides the antibody with ~~and has~~ a KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000

Both of Alexion's additional limitations should be rejected.

1. Adding "in a preexisting antigen-binding domain" to the claim language is improper

Alexion argues that the Court must make clear that the claimed "histidine substitutions" occur "in a preexisting antigen-binding domain." (Alexion '623 Argument at 92-93.) In doing so, Alexion devotes considerable space to analyzing the meaning of "substitution" in the abstract. (*Id.* at 94.) As explained by Dr. Williams, however, "histidine substitutions" has a clear meaning to a person of ordinary skill in the art. (Williams '623 Decl. ¶ 12.) *See Phillips*, 415 F.3d at 1313 ("A court construing a patent claim seeks to accord a claim the meaning it would have to a person of ordinary skill in the art at the time of the invention.") (citation omitted). Specifically, a person of ordinary skill in the art would understand that histidine can be inserted into an antibody at various positions, including in the heavy chain or light chain variable region, and can replace other amino acids in an antibody depending on the application. (Williams '623 Decl. ¶ 12.) Accordingly, a person of ordinary skill in the art would understand that the claimed antibody must have one or more histidine substitutions in the heavy chain variable region or light chain variable region and would understand what that means without further explanation. (*Id.*) Under Chugai's construction, the jury will understand that the claim requires the antibody to have "one or more histidine substitutions" in the variable region, and "substitution" is therefore not read of out of the claim as Alexion suggests.

Moreover, Alexion's proposal to add "in a preexisting antigen-binding domain" conflicts

with the specification and does not capture the full scope of this term. The specification draws a distinction between "pre-existing" antibodies and other kinds of antibodies into which a histidine substitution could be made, e.g., "antibodies and libraries that are prepared from hybridomas," ('623 patent, col. 40:60-63), a fact recognized by Alexion. (*See* Alexion '623 Argument at 93 (specification discloses the "use of ***preexisting antibodies***, preexisting libraries, ***new antibodies***, or new libraries by which mutated antibodies are generated ***by substituting histidine into the above-described antibodies and libraries***") (emphasis added).) Pre-existing antibodies are just one category of antibodies where a histidine substitution can be made. Thus, injecting the word "pre-existing" into the claim language would improperly limit the claims, because it would fail to capture the full scope of "histidine substitution," as informed by the specification. Alexion's proposal should therefore be rejected. *See Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1354 (Fed. Cir. 2004) ("Because the district court did not give the claim language its full scope and customary meaning, this court reverses the district court's claim construction order.").

2. Adding "whereby the histidine substitution provides the antibody with [the KD ratio]" to the claim language is improper

Construing the claims to require that the histidine substitution "provides" the claimed KD ratio, as Alexion proposes, would improperly inject a causation element into the claims, and the proposal reflects a mischaracterization of the intrinsic evidence, a misunderstanding of the scientific principles behind antibody-antigen binding, and a disregard of claim construction law.

a. The claims of the '623 patent do not require a pre-defined, causal relationship among the recited antibody characteristics

Contrary to Alexion's assertion, Chugai has never contended that the histidine

substitution and KD ratio are "unrelated." (Alexion '623 Argument at 81.) Indeed, Chugai stated in its opening brief that "Chugai does not dispute that the inclusion of histidine in the recited antibody *contributes* to the KD ratio for the antibody." (Alexion '623 Argument at 90 (emphasis in original).) The fact that histidine substitution and KD ratio have a relationship, however, does not mean that the claims must be construed to reflect that relationship, and Alexion cites no authority in support of its misguided effort to do so. Moreover, Alexion's attempt to quantify that relationship, i.e., histidine must cause the KD ratio to rise above 10 (for claim 9), is even further untethered from claim construction principles. All that the claim requires, by its plain and unambiguous language, is that the recited antibody possess the three characteristics delineated in the claim. Alexion's proposal to restrict the claim scope to a quantitative functional relationship has no basis in law or evidence and should be rejected.

While Chugai agrees that histidine substitution plays a role in the antibody attaining the KD ratio, it is decidedly not the case that the histidine substitution of the claims must bring the KD ratio of an antibody from outside the claimed range to inside the claimed range, as Alexion contends. The intent of the claimed histidine substitution is to improve the KD ratio to better facilitate antibody recycling. (*See, e.g.*, '623 patent, col. 9:61-66; col. 5:26-37.) Whether the KD ratio, pre-histidine, was inside or outside the claimed range is irrelevant. The patent does not teach a magic KD ratio above which only histidine-substituted antibodies may venture, which is the essence of Alexion's strained construction. Instead, the patent teaches that histidine substitution can improve or enhance the KD ratio to result in better pharmacokinetics. (*See* '623 patent, col. 29:30-38 ("The site into which the histidine or nonnatural amino acid mutation is introduced is not particularly limited and may be any site, as long as the antigen-binding activity at pH 5.8 is weaker than that at pH 7.4 (the KD(pH5.8)/KD(pH7.4) value is greater… as

compared to before substitution."); *see also id.* col. 13:21-26.) Thus, the patent teaches that the KD ratio is intended to become "greater" with the histidine-substituted antibody compared to before the substitution. No mention is made anywhere in the specification that the histidine substitution must cause the KD ratio to increase to a specified level, as urged by Alexion.

Alexion's "hypothetical" does nothing to support its position and highlights Alexion's true motive in proposing its construction. (Alexion '623 Argument at 100.) Alexion plainly wants a construction that would inoculate the accused ravulizumab product (a histidine-substituted antibody) from infringement by excluding from claim 9 any histidine-substituted antibodies whose precursor antibodies (without histidine) already had a KD ratio above 10.[51] Claim 9, however, places no limits on the KD ratio of any precursor antibody; all the claim requires is that the recited antibody have defined characteristics, including one or more histidine substitutions and a KD ratio of 10 to 1,000. ('623 patent, claim 9.) The provenance of the recited antibody and any precursor KD ratios are irrelevant to the scope of the claim. Under Alexion's construction, if a precursor antibody has a KD value of 20 and histidine substitution brings the KD ratio to 21, the antibody would not be covered by the claims, even though the histidine substitution did precisely what Alexion says it is supposed to, i.e., raise the KD ratio. The same would be true for a change in KD ratio from 20 to 999, an enormous boost that, even if attributed solely to histidine substitution, would not be covered by claim 9 according to Alexion, because the precursor antibody already had a KD ratio greater than 10. Alexion's position must be rejected. Indeed, the patent applicants envisioned the very scenario that Alexion argues

[51] The accused product in this case, Alexion's Ultomiris (ravulizumab), is an improvement over its predecessor, Soliris (eculizumab). One reported measurement of eculizumab indicates a KD ratio of 19, and after making histidine substitutions and other changes, the resulting ravulizumab was reported to have a KD ratio of 93. With the improved KD ratio, ravulizumab recycles more effectively within a patient's body, allowing dosing every 8 weeks instead of every 2 weeks.

should be outside of the claim scope and explained that such a scenario is very much within the scope of the invention. (*See* Parren '623 Decl. Ex. 8 at 11 ("Applicant discloses how a variant of a parental antibody that already has the ability to remove antigen from plasma can *more effectively* remove antigen from plasma when the variant has a greater KD(pH5.8)/KD(pH7.4) value than the parental antibody. Thus, even if an increase in KD(pH5.8)/KD(pH7.4) value is subtle, the variant antibody is still expected to remove antigen from plasma at least as well as, but likely better than, the parental antibody.") (emphasis in original).)

In sum, the claims do not require a causal relationship among the recited antibody characteristics and do not require the specific numerical causation that Alexion proposes.

b. Even if the "cause" of the claimed KD ratio is considered, histidine substitution is a non-exclusive, contributing factor, not the sole cause that Alexion's construction requires

Even if causation is considered, Alexion's position that histidine substitution is the sole cause of the claimed KD ratio is wrong. (Alexion '623 Argument at 92 ("[T]he histidine substitution must be what provides the antibody with the claimed KD ratio.").) Although Alexion tries to distance itself from the interpretation that histidine substitution must be the sole cause that provides the antibody with the claimed KD ratio, (*id.* at 11), Alexion's theory cannot be squared with any other interpretation. How, for example, can the histidine substitution be said to "provide the antibody with the claimed KD ratio" if other substitutions also contribute to the claimed KD ratio but are not mentioned in the claim construction? Alexion has no answer to that question because it reveals the inconsistency in its position: on one hand, Alexion states that "a plethora of factors may affect binding affinity," but on the other, states definitively that "the histidine substitution provides the antibody with the claimed KD ratio." (*Id.* at 15.) Alexion's vacillation aside, scientific principles of antibody-antigen binding, the intrinsic evidence, and

claim construction principles all dictate that the claimed histidine substitution is, if anything, a non-exclusive, contributing factor to the claimed KD ratio.

As explained in Chugai's opening brief, the KD ratio of an antibody at two different pH values is the result of the overall composition of the antibody, not a single amino acid. (Williams '623 Decl. ¶ 14.) While the histidine substitutions recited in the claims play an important role in the association and dissociation of the recited antibodies from their target antigens, histidine alone does not dictate the KD values. (*Id.*) The role of histidine in the overall antigen-binding properties of an antibody is influenced by other local side chains in the antibody and the orientation of those side chains with respect to the structure of the antibody. (*Id.*) Alexion's position that the claimed KD ratio is provided solely by histidine substitution is therefore contradicted by scientific principles.[52]

Alexion's position is also refuted by the intrinsic evidence, which Alexion mischaracterizes in an effort to bolster its construction. None of the passages from the specification on which Alexion relies support Alexion's position that histidine substitution must be *the* cause of the claimed KD ratio. At most, the passages support the concept that histidine substitution will *contribute* to a rise in KD ratio, by "increasing the number of times of antigen-binding" and "increasing the ability…to eliminate antigen in plasma," a point that Chugai does not dispute. (Alexion '623 Argument at 82-83 (citing '623 patent, col. 9:61-66; col. 5:26-37).) Alexion touts "the crucial role of the histidine substitution to the KD ratio," but none of the four passages that Alexion cites from the specification support this claim. (*Id*. at 94.) The first

[52] Chugai strongly disagrees with Alexion's assertion that antigen-antibody binding is "unpredictable," which is belied by Alexion's own predictive statements about such binding, e.g., "[i]n most instances, that approach will not work." (Alexion '623 Argument at 2, 4.) The predictability of antigen-antibody binding, however, is not an issue to be resolved on claim construction.

passage, the "Problems to be Solved by the Invention," does not even mention histidine. ('623 patent, col. 3:35-48.) The second and third passages reflect histidine embodiments among dozens of other enumerated embodiments that do not require histidine. And even the embodiments cited by Alexion do not require histidine substitution, disclosing histidine insertion as an alternative. (*Id.* col. 4:11-16; col. 5:26-38.) The fourth passage, (*id.* col. 10:59-11:3), again discloses one embodiment, among other embodiments, where histidine substitution is an option alongside histidine insertion. And the very next sentence makes clear that substitution of amino acids in the constant region (not limited to histidine) is also contemplated by the invention as a means of increasing the KD ratio. (*Id.* col. 11:3-8 ("[T]he present invention provides methods for increasing the ability of an antigen-binding molecule to eliminate antigens in plasma through substituting, deleting, adding, and/or inserting amino acids in the antibody constant region of antigen-binding molecule.").) The alleged "crucial role" of the histidine substitution is not borne out by the evidence. Likewise, Alexion is flatly wrong to assert that "the only mode for improving the pharmacokinetics" is "substituting histidine in the antigen-binding molecule." (Alexion '623 Argument at 94-95.) The passage on which Alexion relies discloses substituting histidine "or inserting" histidine into the antigen-binding molecules. ('623 patent, col. 9:61-66.) And once again, the next sentence reveals that "substituting, deleting, adding, and/or inserting" other amino acids is also a mode of carrying out the invention. (*Id.*, col. 9:66-10:4.)[53]

[53] Another of Alexion's mischaracterizations is its citation to "'623 patent at 59:41-53" in support of the assertion that "[t]he patent explains that the antibody is engineered through the substitution of histidine to maintain binding under plasma pH conditions (pH 7.4) but causes reduced binding under endosomal pH conditions (pH 5.8)." (Alexion '623 Argument at 94.) The cited passage does not even mention histidine. Instead, the passage generally describes "modifications" to an antibody that affect antigen binding such that pharmacokinetics are improved. The patent discloses several such modifications, only one of which is histidine substitution. Alexion is therefore wrong to argue that the patent discloses histidine substitution

Other evidence from the specification further undermines Alexion's position. For example, the specification states that "[a]lternative methods for impairing the antigen-binding activity of an antigen-binding molecule at pH 5.8 as compared to that at pH 7.4 include methods of substituting non-natural amino acids for amino acids in an antigen-binding molecule or inserting non-natural amino acids into amino acids of an antigen-binding molecule…. Such non-natural amino acid substitution and/or insertion ***may be introduced simultaneously with the histidine substitution*** and/or insertion described above." ('623 patent, col. 14:1-14 (emphasis added)). This passage makes clear that precursor antibodies may be modified with both histidine substitutions and non-histidine substitutions to arrive at the desired KD ratio, refuting Alexion's position that it is the histidine substitution that provides the claimed KD ratio. (*See also id.* col. 13:30-35; col. 13:63-67; col. 22:54-57; col. 29:45-49; col. 30:15-23.)

Alexion's reliance on specific antibody examples from the specification fares no better. Alexion relies on the H170 and CLH5 antibodies to argue that "the histidine substitutions are involved in each antibody attaining the KD ratio of claims." (Alexion '623 Argument at 96) Both of these antibodies, however, were additionally substituted with other amino acids. (*See* '623 patent, col. 64:64-65:4 ("H32, H58, H62 and H102 in H3pI…were substituted with histidine, and H95 and H99 ***were further substituted with valine and isoleucine***, respectively, ***to produce H170***.") (emphasis added); *see also id.*, Table 1; *id.*, col. 49:5-10 (CLH5 substitutions); *id.*, col. 69:10-14 ("The pH-dependent binding clones, particularly H170/L82 and CLH5/L73…were demonstrated to be able to repeatedly bind to roughly four times the amount of antigens bound by WT.") Alexion's position that the histidine substitution provides the

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as *the* cause of the claimed pH-dependent binding or as "the fundamental feature" of the invention. (*Id.*) Alexion's cited cases are inapposite for this reason. (*Id.* at 98.)

claimed KD ratio cannot stand.

Finally, Alexion's proposal to limit the claims to KD ratios caused only by histidine substitution is contrary to claim construction law. Alexion's effort to minimize the importance of the "comprising" language in the claims must be rejected. (Alexion '623 Argument at 101-102.) *See Invitrogen Corp. v. Biocrest Manufacturing, L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) ("comprising" allows for additional steps). Although Alexion pays lip service to the idea that other components may "contribut[e] to the KD value under neutral and acidic pH conditions," its proclamation that "the change in the difference in the KD value between neutral and acidic pH results from the histidine substitution" precludes such other components from contributing to that change, which is contrary to both the teachings of the specification and the legal import of the "comprising" language. (*Id.* at 103.) Alexion's reliance on the prosecution history to limit the claims also misapprehends the law. Alexion cites a passage in the file history where the applicants state that the claimed KD ratio is "conveyed ***in part*** by the presence of the additional histidine residue or residues." (Alexion '623 Argument at 97 (quoting Parren '623 Decl. Ex. 8 at 18) (emphasis added).) The applicants' inclusion of "in part" contradicts Alexion's position that histidine alone provides the claimed KD ratio. Thus, Alexion has failed to present any evidence of prosecution disclaimer. *See 3M Innovative Props. Co. v. Tredegar Corp.*, 725 F.3d 1315, 1325 (Fed. Cir. 2013) ("[I]n order for prosecution disclaimer to attach, the disavowal must be both clear and unmistakable.").

For the foregoing reasons, Alexion's proposed construction should be rejected.

XI. ALEXION PHARMACEUTICALS, INC.'S SUR-REPLY CLAIM CONSTRUCTION BRIEF FOR UNITED STATES PATENT NO. 10,472,623

A. Chugai's Reply asks the Court to disregard intrinsic evidence and to construe the claims in a vacuum

Chugai asserts that its proposed construction aligns with the plain meaning because the claims do not recite an express relationship between the claimed histidine substitutions and KD ratio. According to Chugai, a POSITA would not understand there to be a link between the replacement of an existing amino acid with a histidine and the antibody's KD ratio at differing pHs. In pressing this argument, Chugai leaves unanswered the precedent Alexion cites, which requires that when a specification shows that a structure/function relationship is fundamental to an alleged invention, it is proper to construe the claims to include that relationship (discussed *infra*). In its Reply Brief, Chugai essentially admits that the histidine substitution is fundamental to antibody binding, with the improved pharmacokinetics reflected by the KD ratio. *See Supra* at 106-109. Yet despite repeatedly citing the specification's explanation for substituting a histidine for a non-histidine amino acid in the variable region of the antibody, Chugai inexplicably concludes its argument with the assertion that "the claims do not require a causal relationship among the received antibody characteristics." *Id*. at 109. To accept Chugai's position, the Court has to disregard the intrinsic evidence and the relevant case law.

1. The purported purpose of substituting histidine into a variable region is to improve the pharmacokinetics of the antibody by impacting binding at different pHs

At the outset of its paper and in the conclusion of its argument, Chugai remains steadfast that no causal relationship or nexus exists between histidine substitution and the KD ratio. *Supra* at 103-104 and 109. But when discussing the specification's teaching concerning the purpose of a histidine substitution into an antibody's variable region, Chugai agrees and repeatedly

acknowledges that histidine substitution plays a crucial role with respect to the properties of the antibody.[54] *Supra* at 107 ("Chugai agrees that histidine substitution plays a role in the antibody attaining the KD"); *see also supra* at 108, 109, 111. Chugai also admits that the patent describes "that histidine substitution can improve or enhance the KD ratio to result in better pharmacokinetics."[55] *Supra* at 107-108, citing '623 patent, 29:30-38, 13:21-26. The purpose of the histidine substitution is to increase the KD ratio. *Supra* at 107-108. Chugai alleges that an increased KD ratio associated with a histidine substitution "increase[s] the number of times of antigen-binding" and "increase[s] the ability . . . to eliminate antigen from plasma." *Supra* at 110-111. But to conclude that the claims do not require a causal relationship between a histidine substitution and the KD ratio, a POSITA would have to discount these teachings.

Chugai provided only a cursory response to the case law from the Federal Circuit and this District cited by Alexion (*see Praxair*, 543 F.3d at 1306; *AVM Technologies, LLC*, 2016 WL 4182740 *6-*9; *Microsoft Corp.*, 357 F.3d at 1347-48; *Alloc, Inc.*, 342 F. 3d at 1370) by reading the cases narrowly to assert that the histidine is not "'the fundamental feature' of the invention" and that the cases are therefore inapposite. *Supra* at 111, Fn. 53. Chugai is wrong for two reasons. Chugai admits that "the intent of the claimed histidine substitution is to improve the KD ratio to better facilitate antibody recycling." *Supra* at 107, citing '623 patent, 9:61-66, 5:26-

[54] Chugai often states that the purpose of the histidine substitution is to enhance recycling of the antibody. *See supra* at 107. Although the specification states that an increased KD ratio may lead to enhanced antibody recycling, antibody recycling is not a limitation of the asserted claims.
[55] When discussing histidine's role in antibody-antigen binding, Chugai attempts a preemptive defense of the asserted claims in light of the requirements of 35 U.S.C. § 112. *Supra* at 110, Fn. 52. Chugai disagrees that the effect on binding when modifying the amino acids in the variable region is unpredictable. It supports this position by pointing to Alexion's assertion that most often a histidine modification in the variable region would not achieve what the patent alleges would occur. Effectively, Chugai asserts that a method is predictable if it predictably fails—except, of course, for the unpredictable times when it works.

37.[56] Having admitted this fact, Chugai cannot credibly argue that the histidine substitution is not a fundamental feature of the alleged claimed invention. Chugai also appears to read the cases cited by Alexion too narrowly: Chugai concludes that if the alleged invention describes other features, then the cases cited by Alexion do not apply. The analysis in *AVM Technologies* demonstrates the weakness of this argument. *AVM Technologies, LLC*, 2016 WL 4182740, at *3 (rejecting patentee's argument that a narrow construction reads limitations into the claim and construing the claim limitation to achieve the purpose that the specification described for the "clock signal"), *4 (looking at what was contemplated by the specification), *6 n. 7 (rejecting an attempt to expand the scope of the invention beyond that contemplated by the specification). Chugai's patent states that the histidine substitution affects the KD ratio. Any proper construction for claim 9 should reflect this nexus.

Chugai's arguments concerning the specification's discussions of inserting a histidine, i.e., adding a separate histidine into the variable region, and substituting or inserting a non-natural amino acid to alter binding, are irrelevant to claim 9 and its dependent claims. These general statements do not alter the teachings in the specification that the purpose of substituting a histidine is to alter the *in vivo* activity of an antibody by increasing the KD ratio. Moreover, the claims do not include these other purported methods of improving an antibody.

Finally, unable to address the hypothetical Alexion presented in its Answering Brief, Chugai just ignores it. *Supra* at 100-101. Notably, Chugai never explains why the scope of claim 9 should encompass a histidine substitution that does not change or that reduces the KD

[56] Alexion cites to these sections of the '623 patent when asserting that the above-cited cases apply because the specification explains the link between a histidine substitution and the KD ratio. *Supra* at 94 (discussing the problem to be solved and the means of solving it).

ratio.[57] If no relationship exists between the claimed histidine substitution and the claimed KD ratio, then the scenarios in Alexion's hypothetical fall squarely within Chugai's construction. Chugai's inability to address these situations should point the Court to the conclusion that Chugai's construction must be wrong.

In an apparent effort to obfuscate, Chugai proffers its own hypothetical to challenge Alexion's construction that the histidine substitution in the variable region of an antibody provides the antibody with the claimed KD ratio. *Supra* at 108-109. But when considering the specification, Chugai's hypothetical falls flat. Each of the handful of examples in the patent that allegedly support claim 9 demonstrates that the KD ratios for pre-existing wild-type antibodies are lower than the lowest KD ratio of the range of claim 9, and that the KD ratios for antibodies engineered to include histidine increase to potentially fall within that range. *See* '623 patent, 66, Table 5[58], 83, Table 14, 84, Table 16, 85, Table 17. A comparison that focuses on a histidine substitution's effect on changes near the upper limit of the range is not meaningful, because the patent explains "the upper limit of the KD(pH5.8)/KD(pH7.4) value is not particularly limited." *Id*., 12:34-36. That is not true for the lower limit, because the patent purports that achieving a KD ratio that falls above a certain specified range improves the ability of the antibody to remove antigen. The Court should reject Chugai's attempts to disconnect the claim limitations and should conclude that it is the histidine substitution that provides the antibody with the recited KD

[57] Chugai suggests that Alexion's hypothetical is an attempt to manufacture a non-infringement defense. *Supra* at 108. This is incorrect. Alexion's hypothetical shows the disconnect between Chugai's construction and the intrinsic evidence.

[58] Seeking to downplay the importance of the histidine substitution, Chugai states that the IL-6R antibodies have numerous non-histidine substitutions so it is unknown why the antibodies have a higher KD ratio. Alexion agrees this is important—but for a different reason. It further evidences the weakness of the patent's disclosure to support broad claims encompassing all antibodies with the recited characteristics of the claims, because a POSITA would not understand what modifications disclosed for the IL-6R antibodies achieve the claimed characteristics.

ratio.

In addition to seeking to disconnect the claim limitations, Chugai appears to seek to expand the meaning of "histidine substitution." Chugai and its expert suggest that the term "histidine substitution" has a definition well understood to a POSITA. That definition includes two separate manipulations described as distinct in the specification: (1) inserting a histidine into an existing antibody amino acid sequence; and (2) replacing an amino acid in an existing antibody amino acid sequence with histidine. *Supra* at 105 citing Williams '623 Decl. ¶ 12. The Court should reject Chugai's definition because it ignores the term's plain meaning and the specification's unambiguous teachings that a substitution, i.e. replacement, and an insertion are distinct antibody engineering methods. '623 patent, 4:11-16, 5:26-38, 9:55-66, 10:11-16, 11:25-37, 13:9-39, 45:22-30. Chugai itself relies upon this distinction to assert that Alexion's argument concerning the functional nexus between the histidine substitution and the KD ratio of the claim is misplaced. *Supra* at 111. Therefore, the Court should reject Chugai's attempt to conflate (1) replacing and (2) inserting a histidine when defining "histidine substitution."

Chugai's own expert's statements support Alexion's position that a pre-existing antigen-binding domain is the site of a histidine substitution. Dr. Williams opined that a POSITA would understand "that histidine can be **inserted into an antibody** . . .and can **replace other amino acids in an antibody**." Williams '623 Decl. ¶ 12 (emphasis added). A necessary prerequisite to inserting a histidine into an antibody or replacing an amino acid in an antibody is that there exists a starting antigen-binding domain to provide a site for the insertion or replacement.

The specification's explanation that a POSITA can use a pre-existing antibody or a new antibody to engineer the histidine-substituted antibody would not alter a POSITA's view that something must exist at the beginning. It simply expresses that a POSITA can take a known

antibody or can generate a new antibody and use either as the basis to create a histidine-substituted antibody. To avoid confusing a jury, the Court's claim construction should explain that substitution requires replacing an amino acid in a pre-existing antigen-binding domain.

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